

American Heart Journal

VOL. 38

JULY, 1949

No. 1

Original Communications

THE MEASUREMENT OF CORONARY BLOOD FLOW, OXYGEN CONSUMPTION, AND EFFICIENCY OF THE LEFT VENTRICLE IN MAN

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THE introduction of the nitrous oxide method by Kety and Schmidt¹ has made it possible to determine the cerebral blood flow in dog and man. Eckenhoff and Goodale and their associates^{2,3} have recently adapted this method for the measurement of coronary blood flow in the dog by collecting coronary venous blood through a catheter inserted into the coronary sinus. Catheterization of the coronary sinus in man has been successfully performed in a large series of cases.⁴ It therefore seemed feasible to attempt the measurement of coronary blood flow in the human heart using the nitrous oxide method. This report describes the technique of coronary sinus catheterization and the determination of coronary blood flow in man. The findings will be discussed with reference to the extraction and consumption of oxygen and the liberation and utilization of energy in the normal and the diseased heart.

Anatomical Considerations.—The coronary sinus of man is situated in the posterior sulcus of the heart. It extends from the end of the great cardiac vein to its opening into the right auricle. Valves may be situated at its proximal and distal ends. The valve of Vieussens is at the entrance of the great cardiac vein into the coronary sinus, and the valve of Thebesius, at the coronary ostium.⁵ The Thebesian valve is frequently absent. Usually there are no valves in the trunks of these vessels. In addition to these major valves,

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This work was supported by grants from the Commonwealth Fund and from the Carolyn Roso Strauss Foundation, Inc., given to the Department of Surgery, the Johns Hopkins Hospital.

smaller ones are often found at the orifices of the tributary veins. The major veins which contribute to the sinus are the great and middle cardiac veins, the marginal veins, and the vein of Marshall.⁵

The ostium of the coronary sinus is located at the junction of the lower and medial auricular walls (Fig. 1). It is flanked on one side by the auriculo-ventricular foramen and on the other by an endocardial fold, the Eustachian ridge.⁵ The latter structure, which is the rudiment of the right sinus valve, is subject to numerous variations. In the adult heart it may be more than 1.0 cm. in height (Fig. 1), or it may be a perforated netlike structure. It is possible that the Eustachian ridge is largely responsible for the difficulties encountered in the intubation of the coronary sinus.

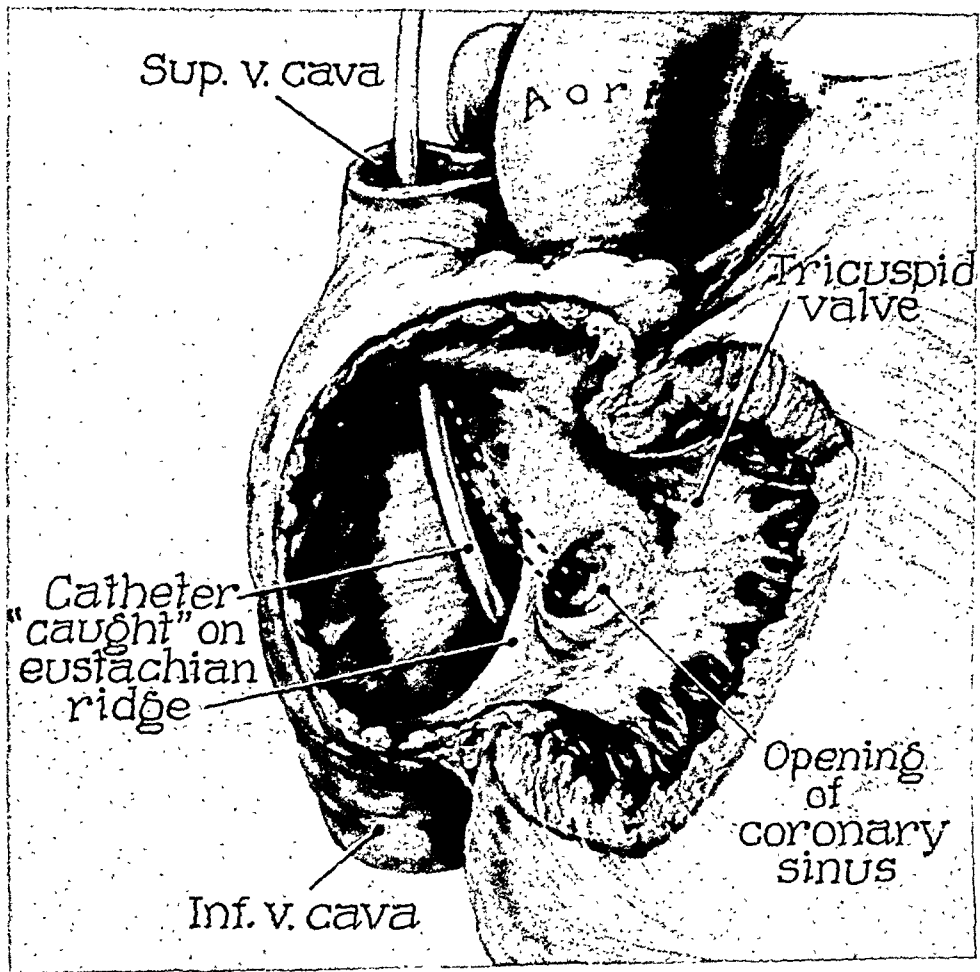


Fig. 1.—The anatomic relationships of the coronary sinus. Difficulties in intubating the coronary ostium are illustrated by showing the catheter caught on the Eustachian ridge.

PROCEDURES

Catheterization of the Coronary Sinus.—The anatomical considerations presented above indicate that catheterization of the coronary sinus in man presents problems which are not encountered during the catheterization of the coronary sinus in the dog or of the right ventricle in man. There are two

difficulties in the procedure. First, the introduction of the catheter into the coronary sinus from the right auricle may be impossible because of the presence of a prominent Eustachian ridge. Second, withdrawal of blood samples from the coronary sinus may be difficult as a result of occlusion of the catheter tip by valves or by the collapse of the walls of the sinus during withdrawal of blood.

To overcome these obstacles, certain modifications of the Cournand standard technique for intracardiac catheterizations in man⁶ were introduced. The sampling difficulties mentioned have been largely overcome by use of a specially designed catheter which has been described elsewhere.³ In addition, a stylette soldered to a Luer-Lok adapter was inserted into the catheter lumen, reaching to within 3 inches of the tip. This allowed the bend at the end of the catheter to remain intact, eliminating the danger of endocardial damage by a protruding wire. The stylette gave the catheter sufficient rigidity to prevent buckling, was airtight, and did not hamper withdrawal of blood.

Despite these improvements in technique, it has not been possible to catheterize the coronary sinus in more than 35 per cent of cases. If the catheter cannot be passed into the ostium of the coronary sinus within twenty minutes, further attempts are useless and should be abandoned. The low incidence of successful coronary catheterizations explains why only twenty-eight successful determinations were made during a two-year period.

Position of the Catheter in the Coronary Venous System.—Four criteria were used to determine that the catheter had entered the coronary sinus. They were: (1) the fluoroscopic position of the catheter, (2) the oxygen content of the coronary venous blood, (3) the pressure in the coronary sinus, and (4) absence of cardiac irregularities.

(1.) Fig. 2 shows the position of the catheter in the coronary sinus. In the anterior-posterior view a similar picture may be obtained with the catheter in the outflow tract of the right ventricle. Failure to guide the catheter into the pulmonary artery, however, suggested that the sinus had been entered. Further insertion of the catheter did not cause buckling, as it would in the right ventricle. It was often helpful to turn the patient into the right lateral position, where frequently a sharp angulation of the catheter could be seen at the coronary ostium. In the dog this observation has been found of great value.³ In man, however, the lateral position was less informative because of variations in the position of the coronary sinus in dilated hearts.

(2.) The oxygen content of coronary venous blood is considerably less than that of mixed venous blood (Table I); therefore, it was often possible to confirm the position of the catheter in the sinus by comparing the color of the blood sample with that of mixed venous blood. If such a comparison is inconclusive, the blood should be analyzed immediately for its oxygen content. An oxygen content of less than 8 volumes per cent is indicative of coronary venous blood.



Fig. 2.—The x-ray appearance of the catheter in the coronary sinus in the anteroposterior position.

(3.) The systolic pressure in the sinus usually does not exceed 14 mm. Hg, whereas the normal systolic pressure in the right ventricle is usually 27 mm. of mercury.

(4.) Irregularities frequently occurred when the catheter tip passed the tricuspid valve or lay against a portion of the medial wall of the right ventricle. Irregularity of the pulse has never been noticed with the catheter in the coronary sinus or the great cardiac vein.

The Measurement of the Coronary Blood Flow.—The principle of the nitrous oxide method outlined by Kety and Schmidt¹ and by Eckenhoff and his associates² was followed. However, several modifications were introduced to adapt the procedure to the measurement of coronary blood flow in man.

Administration of Nitrous Oxide.—Nitrous oxide was administered from a 10-liter anesthesia bag connected to a tank containing a mixture of 15 per cent

TABLE I. DATA ON BLOOD OXYGEN VALUES OF ARTERIAL, MIXED VENOUS, AND CORONARY VENOUS BLOOD

NO.	SUBJECT	SEX	AGE	HGB. (GM./100 C.C.)	O ₂ CONTENT R.V. (VOL. %)	O ₂ CONTENT C.S. (VOL. %)	O ₂ CONTENT F.A. (VOL. %)	A-V O ₂ DIFFERENCE (VOL. %)	
								CORONARY (F.A.-C.S.)	SYSTEMIC (F.A.-R.V.)
GROUP I. NORMAL									
1	W. J.	M	31	13.4	12.9	3.9	17.1	13.2	4.2
2	R. E.	M	55	12.9	12.8	4.9	16.6	11.7	3.8
3	S. S.	M	33	15.0	15.6	6.9	18.9	12.0	3.3
4	I.F.	M	44	10.3	11.6	4.5	13.4	8.9	1.8
GROUP II. ANEMIA									
5	J. B.	M	54	9.0	9.8	3.4	11.5	8.1	1.7
6	J. B.	M	63	8.2	9.1	1.6	10.5	8.9	1.4
7	E. B.	F	21	8.8	7.2	1.7	10.8	9.1	3.6
GROUP III. HYPERTENSION									
9	L. H.	F	68	11.7	11.0	5.3	14.7	9.4	3.7
10	M. L.	F	51	10.5	10.9	3.5	13.4	9.9	2.5
11	G. H.	M	56	13.4	15.0	4.5	17.5	13.0	2.5
GROUP IV. COARCTATION OF THE AORTA									
12	D. M.	M	15	14.2	16.0	6.3	18.4	12.1	2.4
13	P. M.	M	18	14.5	16.3	2.4	18.9	16.5	2.6
14	L. W.	M	32	16.0	17.5	7.1	21.3	14.1	3.1
15	L. M.	F	12	12.6	13.5	2.6	16.2	13.6	2.7
16	C. L.	F	30	12.7	13.3	2.5	16.4	14.1	3.1
GROUP V. CONGESTIVE FAILURE									
17	R. T.	F	37	15.4	13.4	4.7	19.9	15.0	6.3
18	V. A.	F	26	12.9	10.6	4.0	16.6	12.6	6.0
19	C. M.	F	63	15.9	13.6	3.2	18.9	15.7	5.3
26	A. E.	F	38	15.0	14.3	4.3	18.6	14.3	4.3
24	B. C.	M	64	13.1	9.8	3.2	15.6	12.5	5.6
27	W. W.	M	53	14.7	10.7	4.0	17.8	13.8	7.1
MISCELLANEOUS									
Aortic Insufficiency									
20	M. C.	F	35	12.2	12.6	4.0	15.6	11.6	3.0
Aortic Stenosis and Insufficiency									
21	A. G.	M	27	14.1	14.4	6.2	18.1	11.9	3.7
A-V Fistula									
23	J. K.	M	23	13.8	16.3	7.7	17.4	9.6	1.0
Hyperthyroidism									
25	R. H.	M	46	10.8	10.6	4.7	13.4	8.9	3.0
Myocardial Damage									
28	W. B.	M	65	7.2	6.5	3.1	9.6	6.1	3.0

R. V.—Right ventricle.

C. S.—Coronary sinus.

F. A.—Femoral artery.

nitrous oxide, 20 per cent oxygen, and 65 per cent nitrogen. A corrugated respiratory rubber tubing led from this bag to a three-spigot valve and thence to metal T tube containing an inspiratory and expiratory flutter valve as well as a mouthpiece (Fig. 3). The mouthpiece was preferred to a respiratory mask since leakage was less frequently encountered. The patient was allowed to breathe the gas mixture for fifteen minutes to permit full equilibrium of the nitrous oxide with the tissues. After blood samples for oxygen content and nitrous oxide concentration at full saturation had been drawn, the mouthpiece and nose clip were quickly removed.

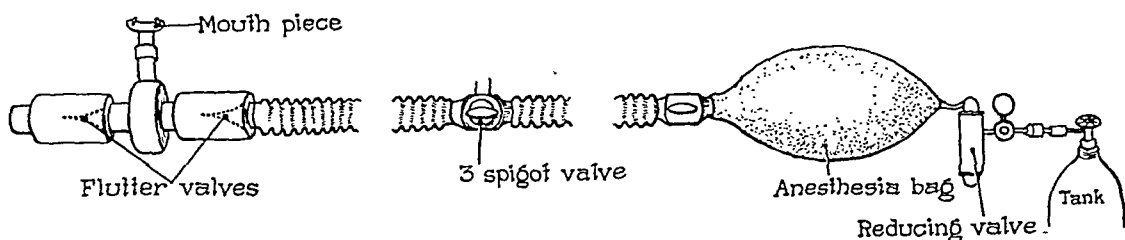


Fig. 3.—The respiratory system for administration of nitrous oxide.

When the method was carried out in this manner, the calculations were based upon a desaturation curve of nitrous oxide as suggested by one of us (W. G.). In the original method, blood samples were taken while the individual was breathing nitrous oxide, resulting in rising nitrous oxide levels. However, this frequently resulted in fluctuations of the nitrous oxide concentrations of the blood due to leakage around the mouthpiece or to respiratory irregularities. These errors were eliminated by use of the desaturation method. In order to calculate the amount of nitrous oxide given up by the heart, it was necessary to subtract the venous level after eight minutes from the venous level at full saturation. The other points on the curve were obtained by subtracting the nitrous oxide concentration of each individual sample from the nitrous oxide concentration at full saturation. This resulted in rising curves similar to those obtained by Kety and Schmidt and by Eckenhoff and his associates, who obtained their samples during the saturation period (Fig. 4).

Preparation of Syringes.—Fifteen dry Luer-Lok syringes of 10 c.c. capacity were autoclaved for sampling of arterial and venous blood, respectively. These were packed with metal sealing caps for the syringes, a beaker of 20 c.c. capacity, and a syringe containing 10 c.c. of Nujol. The set for sampling of arterial blood also contained the manifold described by Kety and Schmidt.¹ As soon as the position of the catheter in the coronary sinus had been ascertained, administration of nitrous oxide was begun and the syringes were prepared for sampling in the following manner:

One 10 c.c. syringe was filled with 5.0 c.c. of a 1.0 per cent heparin solution (Lederle). The oil syringe was emptied into the beaker, and the plunger of each of the remaining syringes was dipped into the oil, which was distributed along the syringe barrel by the plunger. From the heparin syringe, 10 drops of heparin

were introduced into each oiled syringe and distributed along the wall. The manifold was then assembled for collection of arterial blood and a heparin syringe was attached. No manifold was used to sample coronary vein blood.

Sampling of Blood.—The tissues overlying the brachial or femoral artery were infiltrated with 2.0 per cent procaine. An indwelling 19-gauge needle with obturator was then placed in the artery. The manifold system was filled with heparin. Several minutes before the end of the saturation period the obturator was removed and the needle was connected to the manifold with polythene tubing which had been sterilized in Zephiran and rinsed with saline solution.

Just before the end of the saturation period, two samples of both venous and arterial blood were collected, one for determination of nitrous oxide at full saturation and the other for analysis of the oxygen content.

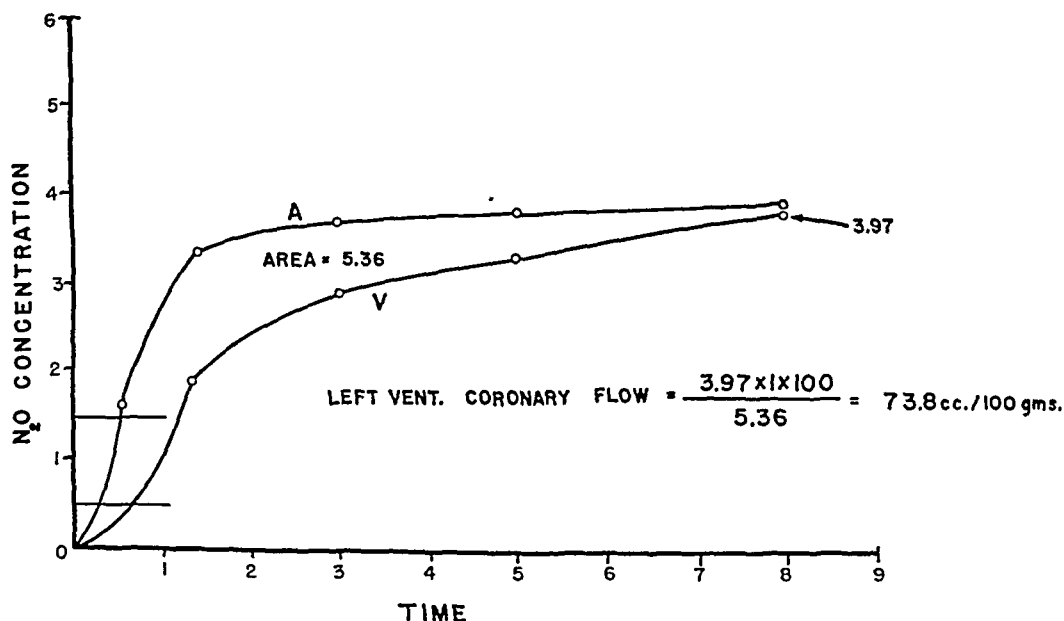


Fig. 4.—The arterial and coronary venous nitrous oxide curves obtained during desaturation. Rising curves are obtained by subtracting each sample from the nitrous oxide concentration at full saturation.

Calculations. — The coronary blood flow was calculated according to the method of Kety and Schmidt except for differences arising from the use of desaturation curves. A partition coefficient of 1 for human heart muscle was used.² The values obtained represented the blood flow per 100 grams of left ventricular muscle per minute.

The oxygen consumption per 100 grams of left ventricular muscle was obtained with the equation:

$$\begin{aligned} &\text{Oxygen consumption per 100 grams of left ventricular muscle per minute} = \\ &(\text{arterial oxygen content volume per cent} - \text{coronary sinus oxygen content vol-} \\ &\quad \text{ume per cent}) \times \\ &\text{left ventricular coronary flow per 100 grams left ventricular muscle per minute.} \end{aligned}$$

It is necessary at this point to discuss the validity of the various calculations involving the oxygen content of coronary venous blood.

It is generally recognized that coronary sinus blood is not true mixed coronary venous blood.⁷ This fact, however, does not detract from the accuracy of determinations computed for 100 grams of cardiac tissue, since the oxygen consumption of and the blood flow through 100 grams of cardiac muscle are obtained only for that portion of the heart from which blood drains into the coronary sinus. It is apparent, however, that contamination of coronary venous blood with *mixed* venous blood will introduce an error. This may be suspected if arterial and coronary venous nitrous oxide concentrations do not approach each other after a desaturation period of eight minutes.

In the calculation of cardiac efficiency, which represents the ratio of work performed to the energy equivalent of the oxygen uptake (the energy cost), a series of assumptions will be made which will be discussed at this point.

1. Values for ventricular work and for energy cost must be obtained for identical portions of the heart. Since it is probable that coronary sinus blood consists of blood which has perfused left ventricular muscle,⁸ the work/energy cost relationship must be calculated for the left ventricle only. It is conceivable, however, that with variations in the ventricular pressures, the coronary sinus contains blood from other portions of the cardiac muscle.⁹ This introduces an appreciable error since then the energy cost and work are not related to the same portion of the heart.

2. In order to obtain the energy equivalent of the oxygen taken up by the heart muscle, a respiratory quotient of 0.82 was assumed. This assumption is based on the work of Macleod.¹⁰ Several direct determinations of the respiratory quotient from coronary blood have given similar values.¹¹ Accordingly, each liter of oxygen consumed releases 2,059 kilogram-meters of energy. The figure thus obtained represents the energy cost per 100 grams of left ventricular muscle.

3. In calculating the relationship of left ventricular work to energy cost, the oxygen consumption of the entire left ventricular muscle must be obtained. This offers serious difficulties, since indirect estimations of the weight of the heart in situ and particularly of the left ventricular muscle must be considered as inaccurate. Smith¹² has compiled a chart relating heart weight, body weight, and sex in normal individuals. The mean values from this chart were used to obtain heart weights of individuals with normal left ventricular work. The left ventricular weight was assumed to be 53 per cent of the total heart weight.¹² Estimations of the left ventricular weight in the presence of cardiac hypertrophy may involve errors as large as 200 to 300 per cent. Consequently, no calculations have been made which utilize this estimate. Instead, the predicted normal left ventricular weight has been used with the understanding that this gives values for total left ventricular oxygen consumption which are lower than the correct values.

The oxygen consumption of the left ventricle was then obtained with the formula:

$$\text{Oxygen consumption of the left ventricle (cubic centimeters of oxygen per minute)} \\ = \frac{\text{left ventricular weight} \times \text{oxygen consumption per 100 grams.}}{100}$$

The efficiency of the left ventricular muscle was calculated according to the equation:

$$\text{Mechanical efficiency (per cent)} = \frac{\text{work of left ventricle (kilogram-meters per minute)}}{\text{energy cost of left ventricle (kilogram-meters per minute)}}$$

The numerator of this equation was obtained using the formula of Starling¹³:

$$\text{Work (kilogram-meters per minute)} = \text{cardiac output (cubic centimeters per minute)} \times \text{mean aortic pressure (cm.Hg)} \times 13.6.$$

No allowance was made in this calculation for the velocity energy, since this component represents less than 10 per cent of left ventricular work.¹⁴

These considerations indicate that values for the coronary blood flow and the oxygen consumptions per 100 grams of left ventricular tissue may be considered accurate under all circumstances. Conversely, in the hypertrophied heart, figures for the oxygen consumption of the whole left ventricle are too low, and hence the calculated efficiency is too high.

Selection of Patients.—Catheterization of the coronary sinus in man was begun only after observations on animals had shown that this procedure was without risk if certain precautions were taken.³ In most instances cardiac catheterization was performed for diagnostic purposes and the left ventricular blood flow was measured after cardiac output had been determined. Consequently, most patients had cardiac abnormalities which required evaluation for surgical or medical therapy. The nature of the procedure was explained to the patient and his written consent was obtained.

In the subsequent paragraphs, patients will be divided into various groups (Tables I and II): Group I, four normal subjects with hemoglobin above 10 grams; Group II, three patients with postoperative hypochromic microcytic anemia (hemoglobin below 10 grams); Group III, five patients with essential hypertension (mean blood pressure above 100 mm. Hg); and Group IV, five patients with coarctation of the aorta. Group V included five patients with congestive heart failure resulting from mitral stenosis and insufficiency, and two with congestive failure due to arteriosclerotic heart disease. In addition to these groups, five patients with various cardiovascular disorders were studied. These included two patients with aortic stenosis and insufficiency, respectively, who showed no clinical or physiologic evidence of cardiac failure. The other patients were: one with an arteriovenous fistula of the femoral artery, one with hyperthyroidism, and one with electrocardiographic and clinical evidence of coronary insufficiency and severe anemia (hemoglobin 6.8 grams). The latter patient had had a coronary occlusion four years preceding the test.

TABLE II. DATA USED IN THE CALCULATION OF LEFT VENTRICULAR EFFICIENCY

NO.	SUBJECT	SEX	AGE	HGB. (GM./100 C.C.)	CARDIAC OUTPUT (C.C./ MIN.)	CARDIAC OUTPUT (C.C./ MIN./M. ²)	AORTIC MEAN PRESSURE (MM. HG.)	L.V. WORK (KG.- METERS)	CORONARY FLOW (C.C./ 100 GM./MIN.)	OXYGEN EXTRAC- TION (VOL. %)	O ₂ CON- SUMPTION/ 100 GM./ MIN.	ENERGY COST L.V. (KG.- METERS)	EFFICIENCY (PER CENT)
<i>GROUP I. NORMAL</i>													
1	W. J.	M	31	13.4	5,400	2,720	87	6.4	55	13.2	7.4	34.1	21.2
2	R. E.	M	55	12.9	4,020	2,440	95	5.2	70	11.8	8.3	22.5	23.1
3	S. S.	M	44	15.0	3,760	2,170	93	4.8	69	12.1	8.3	24.7	19.2
4	I. F.	M	44	10.3	5,150	2,860	93	5.6	66	10.9	7.2	22.8	24.5
<i>GROUP II. ANEMIA</i>													
5	J. B.	M	54	9.0	4,700	3,070	97	6.2	63	8.1	5.1		
6	J. B.	M	63	8.2	8,000	4,570	90	9.8	95	8.9	8.5		
7	E. B.	F	21	8.8	5,220	3,160	77	5.5	84	9.1	7.7		
<i>GROUP III. HYPERTENSION</i>													
9	L. H.	F	68	11.7	7,500	4,440	156	15.8	59	9.4	5.5		
10	M. L.	F	51	10.5	7,350	4,380	130	13.0	64	9.9	6.3		
11	G. H.	M	56	13.4	9,350	4,410	163	19.4	73	13.0	9.5		
<i>GROUP IV. COARCTATION OF THE AORTA</i>													
12	D. M.	M	15	14.2	6,700	3,960	107	9.8	91	12.2	11.1		
13	P. M.	M	18	14.5	6,040	3,230	107	8.8	68	16.2	11.0		
14	L. W.	M	32	16.0	4,775	3,800	127	8.3	58	14.1	8.2		
15	L. M.	F	12	12.6	6,500	4,500	122	11.6	135	13.9	18.8		
16	C. L.	F	30	12.7	4,820	3,070	123	8.0	64	13.8	8.7		

GROUP V. CONGESTIVE FAILURE													
17	R. T.	F	37	15.4	3,025	1,880	78	3.24	54	15.0	8.1	25.1	12.9
18	V. A.	F	26	12.9	3,070	1,890	90	3.76	61	12.6	7.8	21.9	17.1
19	C. M.	F	63	15.9	3,400	2,090	105	4.85	66	15.7	10.4	32.2	15.1
26	A. E.	F	38	15.0	3,800	2,320	82	4.2	75	14.3	10.4	28.8	14.8
24	B. C.	M	64	13.1	3,500	2,120	103	4.8	75	12.4	9.4	34.8	14.1
27	W. W.	M	53	14.7	3,320	2,100	73	3.3	52	13.8	7.2	22.5	14.6
MISCELLANEOUS													
Aortic Insufficiency													
20	M. C.	F	35	12.2	5,900	3,760	92	7.4	93	11.6	10.8		
Aortic Stenosis and Insufficiency													
21	A. G.	M	27	14.1	4,100	2,130	80	4.5	70	11.9	8.5		
Arteriovenous Fistula													
23	J. K.	M	23	13.8	20,590	11,700	65	18.2	84	9.6	8.1		
Hyperthyroidism													
25	R. H.	M	46	10.8	8,700	5,300	90	10.6	85	8.9	7.5		
Myocardial Damage and Anemia													
26	W. B.	M	65	7.2	8,000	5,100	85	10.0	58	6.0	3.5		

Special Techniques.—Blood oxygens were determined by the manometric method of Van Slyke and Neill.¹⁵ The oxygen consumption was obtained from the oxygen and carbon dioxide content of expired air, which was collected in a Douglas bag over a period of one and one-half minutes. The oxygen in expired air was determined with the Pauling oxygen analyzer. The carbon dioxide was determined on the Haldane apparatus. Pressures were optically recorded with strain gauges. The mean pressure was obtained by planimetric integration of the area under the pressure curve.

RESULTS

The Oxygen Content and the Arteriovenous Oxygen Difference of Coronary Blood.—Table I shows that in the normal subjects the oxygen content of coronary venous blood varies from 3.9 to 6.9 vol. per cent. This finding agrees with the result of Eckenhoff and his associates² for the anesthetized dog. Studies in this laboratory on the unanesthetized dog reveal somewhat lower values.¹⁶ The oxygen content of coronary sinus blood was considerably lower than that of mixed venous blood (Table I). The oxygen extraction ranged from 8.9 to 13.2 vol. per cent, with an average of 12 vol. per cent (Table I and Fig. 5).

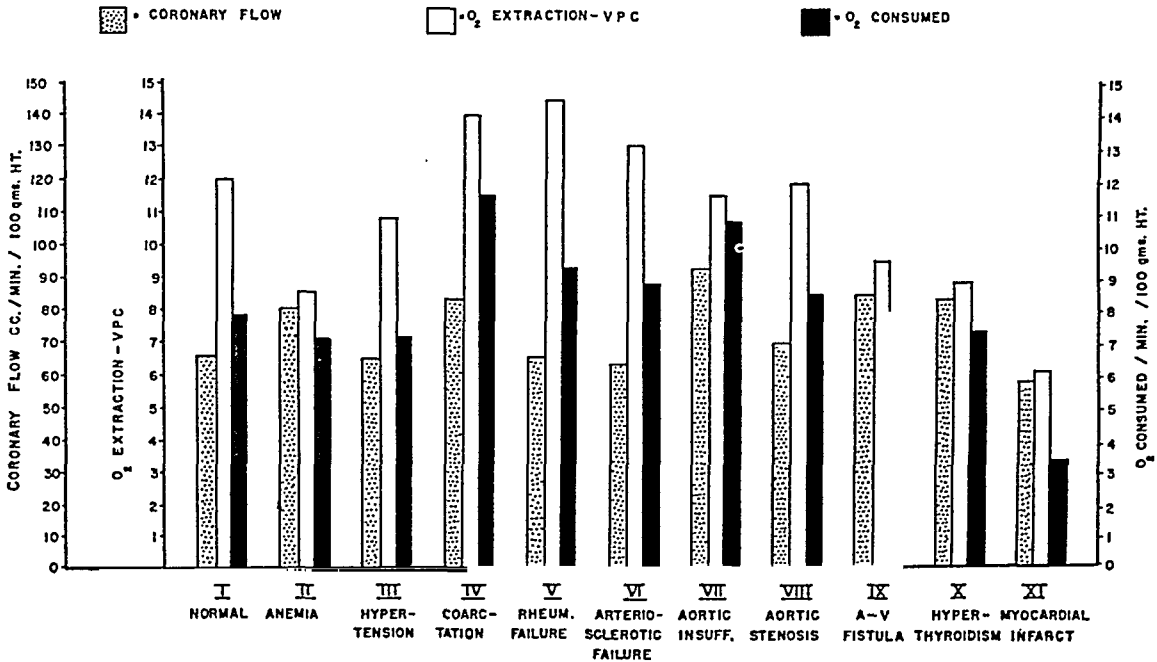


Fig. 5.—Summary of the average values for left ventricular coronary blood flow per 100 grams per minute, oxygen extraction, and left ventricular oxygen consumption per 100 grams per minute obtained in the various groups of patients studied.

In individuals belonging to Group II (anemia) the left ventricular oxygen extraction was smaller, varying from 8.1 to 9.1 vol. per cent, with an average of 8.7 vol. per cent (Table I and Fig. 5). The oxygen content of coronary sinus blood was 1.6 vol. per cent in two patients with a hemoglobin content of 8.2

and 8.8 grams, respectively (Table I). In these individuals the oxygen difference between femoral arterial and mixed venous blood was also significantly reduced (Table I).

It seemed noteworthy that the left ventricular extraction of oxygen in patients with essential hypertension (Group III) was below normal, varying from 9.4 to 13 vol. per cent, with a mean of 10.8 (Table I and Fig. 5). It will be shown that this factor is responsible for decreased left ventricular oxygen consumption per 100 grams found in the patients of this group. The oxygen content of coronary sinus blood in these cases ranged from 3.5 to 5.3 vol. per cent.

In individuals belonging to Group IV (coarctation of the aorta) the oxygen extraction was significantly elevated, varying from 12.1 to 16.5 vol. per cent, with an average of 14 vol. per cent (Table I and Fig. 5). Since the coronary blood flow was normal or increased, the oxygen consumption was significantly elevated. The oxygen content of coronary sinus blood ranged from 2.4 to 7.1 vol. per cent (Table I).

In the patients with mitral stenosis and insufficiency (Group V) the oxygen extraction of left ventricular muscle was significantly elevated, ranging from 12.6 to 15.8 vol. per cent, with a mean of 14.4 vol. per cent (Table I and Fig. 5). The oxygen difference between peripheral arterial and mixed venous blood was also increased (Table I). The oxygen content of coronary sinus blood varied from 3.2 to 4.7 vol. per cent (Table I). The two patients in failure due to arteriosclerotic heart disease had an average oxygen extraction of 13.1 vol. per cent (Fig. 5). The oxygen content of coronary sinus blood averaged 3.6 vol. per cent (Table I).

In the two patients with aortic insufficiency and stenosis the oxygen extraction was 11.6 and 11.9 vol. per cent, respectively (Table I and Fig. 5). The oxygen content of coronary sinus blood was 4.0 and 6.2 vol. per cent (Table I). In the patient with the arteriovenous fistula the oxygen content of the coronary sinus blood was 7.7 vol. per cent, with an extraction of 9.6 vol. per cent (Table I and Fig. 5). The patient with hyperthyroidism had a coronary sinus oxygen value of 4.7 vol. per cent and an extraction of 8.9 vol. per cent (Table I and Fig. 5). The patient with coronary insufficiency and anemia had a coronary sinus oxygen content of 3.1 vol. per cent and an extraction of 6.1 vol. per cent (Table I and Fig. 5).

The Coronary Flow and the Left Ventricular Oxygen Consumption.—The left ventricular blood flow in the normal subjects (Group I) ranged from 55 to 70 c.c. per 100 grams per minute (Table II and Fig. 5), with a mean of 65 c.c., and the left ventricular oxygen consumption per 100 grams ranged from 7.2 to 8.3 c.c. per minute, with an average of 7.8. In the normal anesthetized dog the average left ventricular oxygen consumption was 9.5 c.c. per 100 grams per minute,¹⁸ although the unanesthetized dog revealed considerably higher values.¹⁶

In patients with anemia (Group II) the left ventricular flow was increased (from 62.5 to 95 c.c. per 100 grams per minute, with a mean of 81 c.c.). Be-

cause of the marked decrease in oxygen extraction, however, the oxygen consumption was below normal, with a mean of 7.1 c.c. per 100 grams per minute (Table II and Fig. 5).

In patients with essential hypertension (Group III) the coronary flows were within normal limits, ranging from 59 to 73 c.c. per 100 grams per minute, with an average of 65 cubic centimeters. The left ventricular oxygen consumption per 100 grams was slightly below normal, averaging 7.1 c.c. per 100 grams per minute (Table II and Fig. 5). In contrast, patients with coarctation of the aorta (Group IV) showed a significant increase in the coronary blood flow and the left ventricular oxygen consumption. The left ventricular coronary flow (Table II and Fig. 5) ranged from 64 to 135 c.c. per 100 grams per minute, with a mean of 83 cubic centimeters. The highest flows in this group were recorded in the younger patients. The oxygen consumption per 100 grams of left ventricular tissue was also markedly elevated, the values ranging from 8.2 to 18.8 c.c. per 100 grams per minute, with an average of 11.6 (Table II and Fig. 5).

The left ventricular coronary blood flows in patients with congestive heart failure due to mitral stenosis and insufficiency were normal, ranging from 54 to 75 c.c. per 100 grams per minute, with a mean of 64 c.c. (Table II and Fig. 5). These values may be lower than the true flows because of the failure of the venous curve to approach the arterial as a single exponential function.² This could have been the result of the presence within the cardiac tissue of fat, which has a greater nitrous oxide capacity and consequently a longer saturation time than cardiac muscle. The increased oxygen extraction in these patients was responsible for the fact that the left ventricular oxygen consumption per 100 grams of cardiac tissue was slightly increased (Table II and Fig. 5). The left ventricular oxygen consumption in failure ranged from 8.1 to 10.4 c.c. per 100 grams per minute, with a mean value of 9.2 c.c. (Table II). These findings may not represent true values since the coronary flows were probably too low. However, even if the oxygen consumptions in these four patients were calculated for heart muscle which has been fully equilibrated with nitrous oxide, the values for oxygen consumption would still be less than those observed in the failing heart *in vitro*.⁷ The significance of this finding will be discussed in a subsequent paragraph.

In the two patients suffering from arteriosclerotic heart disease with congestive failure the left ventricular oxygen consumption per 100 grams was 8.3 c.c. per minute (Table II and Fig. 5). The oxygen extraction was normal (13.1 vol. per cent).

In the patient with aortic insufficiency the left ventricular coronary blood flow was 93 c.c. per 100 grams (Table II and Fig. 5). This represents a marked increase above normal values (Table II and Fig. 5). Green and his co-workers¹⁷ also found that the coronary blood flow in aortic insufficiency was markedly increased, provided that the mean aortic pressure was not lowered. The left ventricular oxygen consumption per 100 grams per minute was 10.8 (Table II). This represents a significant increase over the normal.

The coronary flow and the left ventricular oxygen consumption per 100 grams were slightly elevated in the patient with the arteriovenous fistula, being 8.4 c.c. per 100 grams per minute and 8.1 c.c. per 100 grams per minute, respectively (Table II and Fig. 5). In the patient with hyperthyroidism the left ventricular flow and the left ventricular oxygen consumption were only slightly increased, being 84.5 c.c. per 100 grams per minute and 7.5 c.c. per 100 grams per minute, respectively (Table II and Fig. 5). This is surprising since the rise in the oxygen consumption per unit weight should be at least proportional to the total metabolism, which was markedly elevated (+50). In contrast, the left ventricular coronary flow in the patient with aortic stenosis was within normal range, being 70 c.c. per 100 grams per minute (Table II and Fig. 5). This patient had severe anginal pain on exertion, but was symptom free at rest. Apparently the coronary flow, though adequate at rest, could not increase sufficiently during exercise to supply the muscle with an adequate amount of oxygen. The oxygen consumption per 100 grams was within normal limits, being 8.5 c.c. per minute (Table II and Fig. 5).

The left ventricular coronary blood flow in the patient with coronary insufficiency and anemia was 58 c.c. per 100 grams per minute (Table II and Fig. 5). Since the oxygen extraction was only 6.05 vol. per cent, the oxygen consumption per 100 grams of ventricular muscle was 3.48 c.c. per minute. The extremely low values for the coronary flow and left ventricular oxygen consumption are particularly surprising in view of the elevated cardiac output, which was 8,000 c.c. per minute. It was apparent that the left ventricular oxygen consumption, determined by coronary sinus catheterization, was inadequate for the left ventricular work. Therefore, it must be surmised that the coronary sinus contained blood which had perfused scar tissue rather than healthy myocardium. This conclusion is supported by the electrocardiographic and clinical evidence of myocardial damage.

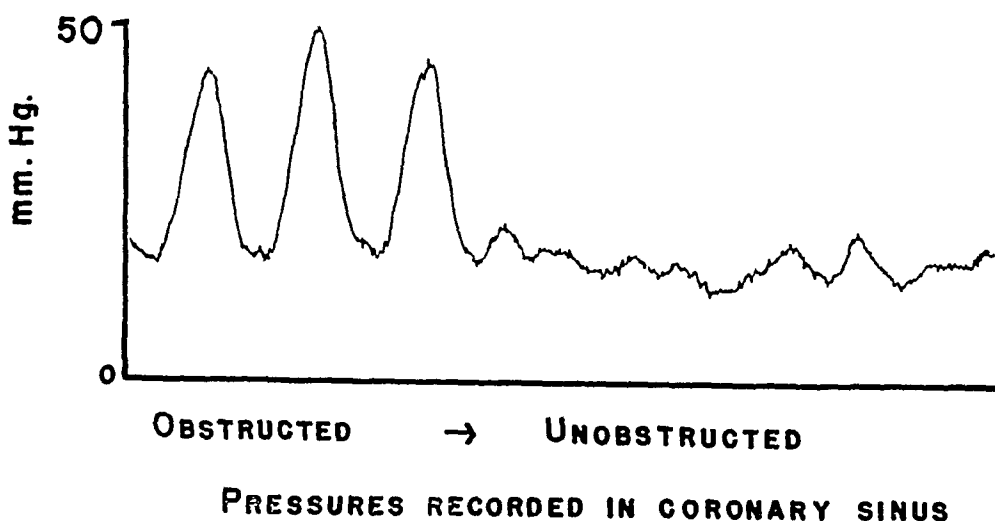


Fig. 6.—An optically recorded pressure tracing from the coronary sinus. The high pressures were obtained when the catheter was obstructing the outflow from the great cardiac vein. The arrow indicates the point at which the withdrawal of the catheter relieved the obstruction.

TABLE III. CORONARY SINUS PRESSURES (Mm. Hg)

SUBJECT	CORONARY SINUS	RIGHT AURICLE
Group I		
W. J.	14/9	
R. E.	13/10	
S. S.	15/6	
E. M.*	24/9	18/9
C. M.*	12/5	7/2
G. R.*	19/9	
B. F.*	18/14	16/13
C. S.*	15/7	
A. W.*	14/12	13/12
U. B.*	17/15	9/8
M. L.*	18/12	
Average	16/8	12/9
Group II		
J. B.	8/0	
J. B.	11/10	
Average	9/5	
Group III		
G. H.	14/6	
M. L.	11/4	
L. H.	11/4	
Average	12/6	
Group IV		
L. W.	11/4	
Group V		
R. T.	18/14	17/14
V. A.	28/15	
B. C.	28/20	
C. M.	10/7	
F. P.*	28/22	
Average	26/16	17/14

*Coronary flow not measured.

Coronary Sinus Pressure.—Pressures recorded from the coronary sinus show that in Group I the average systolic pressure was 16 mm. Hg; the average diastolic pressure, 8 mm. Hg (Table III). These findings confirm those reported in a previous communication.⁴ Smaller values were obtained in Group II.

In contrast to these findings were those obtained in the patients with cardiac failure. Here the average systolic pressure was 21 and the average diastolic pressure 18 mm. of mercury.

A typical pressure tracing, recorded from the coronary sinus, is illustrated in Fig. 6. This tracing shows two different patterns; one follows closely the typical tracing obtained from the right auricle of man.¹⁹ Two positive waves can be recognized. It is probable that these peaks correspond to the *a* and *c* waves seen in right auricular pressure tracings and are the result of auricular and ventricular contractions, respectively.

A different pattern was obtained in this same patient when the catheter tip was deeply introduced into the coronary sinus (Fig. 6). In this instance, systolic and diastolic pressures were significantly elevated and only one sharp peak, which closely followed the left ventricular ejection period, was recorded. It is possible that this pattern resulted from venous obstruction by the catheter, which permitted the transmission of aortic pressure waves through the capillary bed. Similar results have been obtained in dogs after obstruction of the coronary sinus with the catheter.³

It is, therefore, considered likely that the coronary sinus has no unique pressure pattern and that the observed tracings represent transmission of either auricular or aortic pressure waves.

DISCUSSION

Catheterization of the coronary sinus in man is a difficult procedure. This is primarily the result of anatomical variations in the structure of the right auricle, such as, for example, the presence of an elevated Eustachian ridge (Fig. 1). Although the incidence of successful catheterization of the coronary sinus can be increased by special technical improvements, only 25 per cent of all attempted catheterizations are successful. Despite these technical difficulties, catheterization of the coronary sinus had led to no untoward consequences.

In the evaluation of results presented in this paper, particular emphasis should be placed on a careful differentiation between data calculated directly and those obtained through assumptions. Thus, values for the coronary blood flow through left ventricular muscle and the oxygen consumption per 100 grams of left ventricular tissue may be considered accurate. The fact that coronary sinus blood is not true mixed coronary venous blood does not detract from the accuracy of these determinations, since they obtain only for that portion of the heart from which blood drains into the coronary sinus. Calculations of oxygen consumption of the entire left ventricle and its mechanical efficiency, however, involve estimations of left ventricular weight. This can be obtained only indirectly from tables relating heart weight and body weight, and from the assumption that left ventricular muscle comprises a constant fraction of the total heart weight.¹² It is therefore obvious that figures for the left ventricular energy cost and mechanical efficiency must be approximations. It is probable that calculations for the efficiency of the normal left ventricle are close to the actual values since the weight of the normal left ventricle may be estimated from the tables of Smith¹² with considerable accuracy. However, estimation of the weight of the hypertrophied or dilated left ventricular muscle cannot be made. For these reasons, only calculations of the efficiency of Groups I and V are included. Using maximal normal weights, certain trends in the direction of left ventricular efficiency may be estimated in congestive failure. As was pointed out in a previous section, the use of normal heart weights gives

values for the total left ventricular energy cost which are too low for the hypertrophied heart. Consequently, a high efficiency is not significant. On the other hand, a low efficiency obtained in hypertrophied hearts is of great significance, since the actual efficiency must be even lower. This is the case in congestive failure.

The results indicate that in the normal heart the oxygen content of coronary venous blood is considerably lower than that of mixed venous blood (Table I). Consequently, the coronary arteriovenous oxygen difference is higher than the difference between systemic and mixed venous blood (Table I). The left coronary ventricular blood flow in the normal ranges from 55 to 70 c.c. per 100 grams per minute (Table II and Fig. 5). Similar figures were previously obtained by Eckenhoff and his associates² in the anesthetized dog. Experiments undertaken in this laboratory indicate that the left ventricular coronary blood flow and left ventricular oxygen consumption per 100 grams are twice as great in unanesthetized dogs.²³ It is probable, therefore, that variations in the experimental conditions are largely responsible for the discrepancies observed.

In anemic subjects (Group II) the coronary arteriovenous oxygen difference and the oxygen consumption per 100 grams is reduced (Tables I and II and Fig. 5), while the coronary blood flow is slightly elevated (Table I and Fig. 5). This is of interest since it indicates that the increase in coronary blood flow is insufficient to compensate for the reduction in the coronary arteriovenous difference. Most individuals belonging to this group were only mildly anemic and only one had increased cardiac output (Subject 6, Table II). It is possible that in severe anemia the changes in coronary blood flow are greater. The oxygen content of coronary sinus blood in Patient E. B. (Table I) is only 1.5 vol. per cent. This individual suffered from anginal pain appearing on exercise. Since in this patient the oxygen extraction by the heart muscle is already maximal at rest, the heart must rely entirely on changes in coronary blood flow to fulfill its increased oxygen demand during exertion. Once the coronary flow has reached its upper limit, no further increase in oxygen consumption of the heart is possible. This results in relative cardiac anoxia and may lead to anginal pain.

In patients with essential hypertension (Group III) the oxygen extraction, the oxygen consumption per 100 grams of left ventricular tissue, and the left ventricular coronary blood flow per 100 grams are within normal limits (Tables I and II and Fig. 5). The observation that the coronary blood flow is normal in the presence of increased mean aortic pressure indicates that the vascular resistance in the coronary bed is increased. This finding contrasts with that obtained by Gregg⁸ on the anesthetized dog. This investigator showed that when the blood pressure rose as a result of clamping of the aorta, the coronary minute volume increased with the blood pressure, regardless of changes in cardiac rate and output. The discrepancy between these results suggests an increase in the resistance in the coronary vascular bed of patients with essential hypertension. It is apparent that as a result of cardiac hypertrophy the total

left ventricular oxygen consumption is increased, although the oxygen consumption per unit weight is normal (Fig. 7). Evans,¹⁴ among others, has shown in the heart-lung preparation that a sudden increase in the vascular resistance produced a rise in oxygen consumption per unit of left ventricular weight.

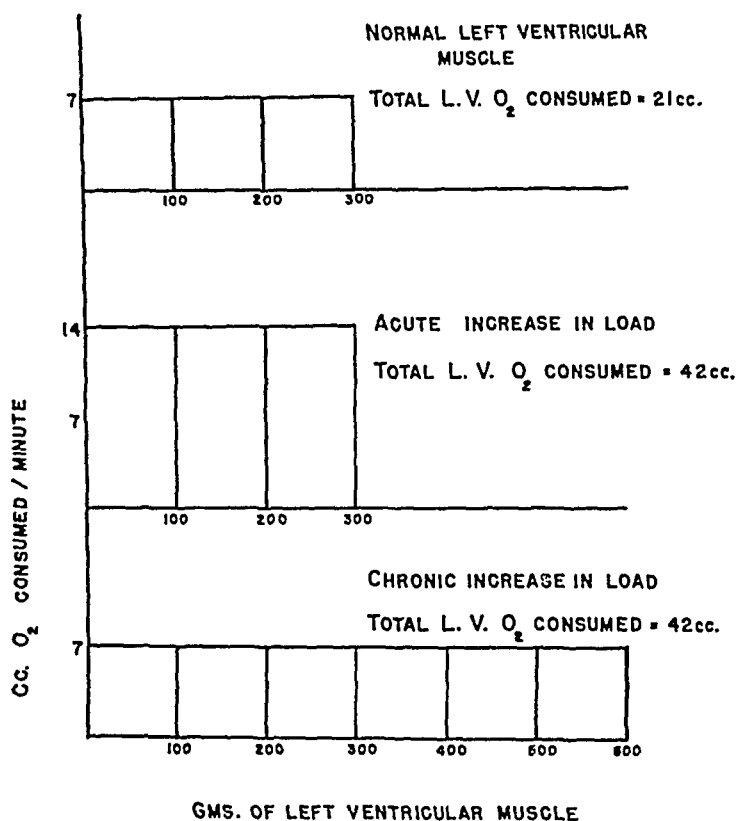


Fig. 7.—Comparison of the response of heart muscle to acute and chronic increase in load. The data for the response to acute increase represent theoretical values similar to those obtained in acute experiments in the heart-lung preparation. The data for the response to chronic increase in load are taken from Group III, assuming a left ventricular weight of 600 grams. It may be seen that in contrast to acute increase in load, a chronic increase results in a rise in the total oxygen consumption while the oxygen consumption per unit of weight remains constant.

In individuals with coarctation of the aorta (Group IV), on the other hand, the average arteriovenous oxygen difference, the left ventricular coronary blood flow per 100 grams, and the cardiac oxygen consumption per 100 grams of left ventricular tissue are markedly elevated (Tables I and II and Fig. 5). Tables I and II illustrate, however, that the coronary blood flow is greatest in the younger individuals. The oxygen extraction and the oxygen consumption per 100 grams of left ventricular tissue, on the other hand, are increased in all patients with this malformation (Tables I and II). These findings differentiate the coronary hemodynamics in coarctation from those in essential hypertension where the oxygen consumption per 100 grams of left ventricular muscle is normal. The observation that the coronary blood flow in the younger individuals of this group is elevated may be due to the smaller heart size. This

would increase the left ventricular coronary flow per unit weight, while the flow through the whole left ventricular muscle remains normal. Spencer and his associates¹⁶ have found a very close relationship between body weight and coronary flow per unit of left ventricular tissue. The increase in left ventricular oxygen consumption per 100 grams found in all patients with coarctation of the aorta is of interest from another standpoint. According to Starling,²⁰ increased diastolic volume results in increased fiber length and consequently in an increased left ventricular oxygen consumption. It is possible, therefore, that in coarctation the diastolic volume of the left ventricle is greater than in compensated forms of essential hypertension. This hypothesis is supported by the finding that pulmonary hypertension has been present in all cases of coarctation studied in this laboratory. This may have been the result of increased diastolic blood volume in the left ventricle.

In the six patients with congestive failure due to arteriosclerotic heart disease and mitral stenosis and insufficiency (Group V) the oxygen consumption per 100 grams of left ventricular tissue is slightly elevated. The left ventricular diastolic volume, on the other hand, is probably increased. This is supported by fluoroscopic evidence of left ventricular enlargement and clinical signs of mitral regurgitation. Starling and Visscher,²⁰ investigating the mechanism of heart failure in vitro, found that the increase in diastolic volume led to a proportional increase in the oxygen consumption per unit weight. It is therefore difficult to explain why only a slight increase in the oxygen consumption per unit weight is present in the patients of this group.

The elevation of the coronary blood flow in the patients with aortic insufficiency and arteriovenous aneurysm (Fig. 5) confirms the finding of Green¹⁷ in experimental aortic insufficiency and arteriovenous fistula. The same investigator found that the coronary flow in severe artificially produced aortic stenosis was markedly reduced. In the patient with aortic stenosis (A. G., No. 2, Table II and Fig. 5), however, the left ventricular coronary blood flow was normal at rest. The observation that this individual had severe anginal pain on exertion, but was symptom free at rest, indicates that the coronary flow could not increase sufficiently during exertion.

A consideration of the results obtained in the patient with myocardial damage is especially important since it raises the question whether or not coronary sinus blood can be considered as representative of blood which has coursed through left ventricular tissue. It was pointed out in a previous paragraph that blood withdrawn from the coronary sinus is assumed to be representative of blood which has perfused left ventricular muscle. In the presence of scar tissue, however, a fraction of coronary sinus blood will not have coursed through normal myocardium and the above assumption will not be valid. In this case, values obtained are probably lower than those for unaffected myocardium, since the scar tissue of the infarct represents an area of low flow and decreased oxygen uptake. It is important to emphasize, however, that the presence of scar tissue can be suspected by failure of the arterial and venous nitrous oxide curves to reach equilibrium within eight minutes.

An analysis of pressure tracings obtained from the coronary sinus shows no characteristic pattern (Table III and Fig. 5). Two types of curves are obtained (Fig. 6), one resembling an auricular, the other a dampened aortic tracing. The latter is obtained when the catheter tip is inserted deeply into the sinus, and probably obstructs the lumen.

The average systolic pressure in the unobstructed coronary sinus varies from 19 to 12 mm. Hg (Table III). In the patients with congestive failure, elevation of the right auricular pressure results in increase in coronary sinus pressure (Table III).

Although the data collected in this report are not numerous enough to permit statistical analysis, they represent two years of observations on the use of a new method. Technical difficulties in the method prevented the study of a larger series of patients. Certain trends are noticeable, however, which will be discussed at this point.

An examination of the relationship between cardiac output and coronary flow reveals some correlation in normal individuals and in the patients with postoperative anemia (Fig. 8). Excellent correlation has been found in the heart-lung preparation and in the normal unanesthetized dog.^{21,16} In patients, however, in whom the cardiac output is elevated over long periods of time, as, for example, in arteriovenous fistula or in hyperthyroidism, the coronary blood flow per unit weight is within normal limits (Fig. 5).

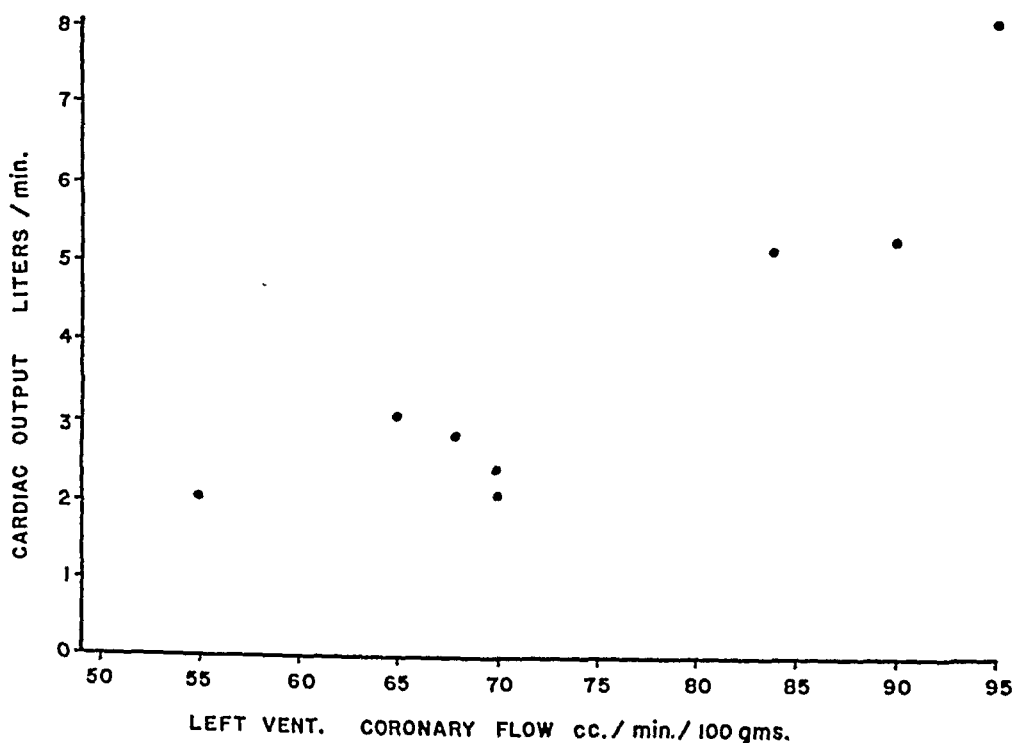


Fig. 8.—The relation between cardiac output and left ventricular coronary flow per unit weight of hearts of normal and acutely anemic individuals (Groups I and II). It can be seen that in these non-hypertrophied hearts the left ventricular coronary flow varies directly with the cardiac output.

In the patients of this series in whom the left ventricular load is elevated as a result of essential hypertension or arteriovenous fistula, the oxygen consumption per unit of left ventricular work remains normal. Starling and Visscher²⁰ among others demonstrated that an increase in load due to increased venous filling or to a rise in resistance results in a rise in the oxygen consumption of the heart. They demonstrated that this was the result of increased diastolic fiber length. Since the weight of the isolated heart remains constant as the load increases, the oxygen consumption per unit weight increases proportionally. The finding obtained in the patients with essential hypertension and arteriovenous fistula demonstrates a different response of the heart to chronic increase in load from that found in acute experiments in the heart-lung preparation. In the latter case the increased metabolic demands of the heart muscle are met by a rise in coronary blood flow or oxygen extraction. In this respect the response of the heart is similar to that of other organs or of the organism as a whole. When, however, the increase in load is prolonged over months or years, the heart meets its increased energy requirements not by a rise in oxygen consumed per unit weight but by an increase in the total weight of its muscle. Thus, in the hypertrophied heart the oxygen consumption per unit weight can be normal, while the total left ventricular oxygen consumption is increased (Fig. 7).

In the six patients with congestive heart failure the oxygen consumption per unit of left ventricular tissue is slightly elevated (Table II and Fig. 5). Four of these had mitral stenosis with some clinical evidence of regurgitation. Two had arteriosclerotic heart disease. The left ventricle in all these patients showed radiologic evidence of enlargement, which was particularly marked in one patient with arteriosclerotic heart disease. Starling²⁰ has shown that acute failure of the heart in vitro was accompanied by a significant increase in the oxygen consumption and a decrease in cardiac output. Since the oxygen consumption per unit weight is not increased in these patients, the diastolic fibers must either remain constant or Starling's concept is not valid. Investigations are now in progress to elucidate this problem further.

The cardiac efficiency of normal left ventricular muscle averages 23 per cent (Table II). This value is considerably higher than that obtained in the heart-lung preparation. The difference is probably the result of the relatively low cardiac output of the isolated dog's heart. When, however, the cardiac output of the dog's heart in vitro is raised to levels comparable to those observed in the normal human heart, the left ventricular efficiency approaches that seen in normal man.¹⁴ An estimation of left ventricular efficiency in hearts with cardiac hypertrophy is impossible for reasons outlined above. When, however, an efficiency, calculated on the basis of normal heart weight, is low, it is significant. This is the case in the six patients with congestive heart failure. Table II shows that the left ventricular efficiency ranges from 10 to 17 per cent. A similar decrease in cardiac efficiency was found by Starling and Visscher²⁰ in the failing heart in vitro. This was the result of decreased cardiac work and of increased cardiac oxygen consumption. Moe and Visscher⁷ in later studies were able to obtain lowered cardiac efficiency in failure by decrease

in cardiac output alone. In these experiments the oxygen consumption of the heart remained constant, since the diastolic volume of the heart was maintained. The assumption may be ventured, therefore, that in certain types of human heart failure, the cardiac efficiency is low.

SUMMARY

The left ventricular coronary blood flow and left ventricular oxygen consumption per unit weight have been determined in twenty-six patients by means of the nitrous oxide method in conjunction with catheterization of the coronary sinus. The studies were performed on normal individuals and on patients with various forms of cardiovascular disease.

The technique of coronary sinus catheterization and of the nitrous oxide method as applied to the coronary circulation in man have been presented.

In the normal subject the left ventricular coronary blood flow per 100 grams per minute and the left ventricular oxygen consumption per 100 grams per minute averaged 65 c.c. and 7.8 c.c., respectively. The average oxygen extraction was 12 volumes per cent.

In acutely anemic patients the left ventricular coronary blood flow per 100 grams per minute was slightly increased, whereas the left ventricular oxygen consumption per 100 grams per minute and the left ventricular oxygen extraction were reduced.

In patients with essential hypertension, left ventricular coronary blood flow per 100 grams per minute, left ventricular oxygen consumption per 100 grams per minute, and left ventricular oxygen extraction were normal.

In patients with coarctation of the aorta, the average left ventricular coronary blood flow per 100 grams per minute, left ventricular oxygen consumption per 100 grams per minute, and left ventricular oxygen extraction were all increased.

In congestive failure due to mitral stenosis and insufficiency and to arteriosclerotic heart disease the left ventricular coronary blood flow per 100 grams per minute, was normal. The oxygen extraction was slightly elevated. Despite clinical and radiological evidence of marked left ventricular enlargement, the oxygen consumption per 100 grams per minute was only slightly elevated.

Left ventricular coronary blood flows per 100 grams per minute were increased in patients with aortic insufficiency, arteriovenous fistula, and hyperthyroidism. The left ventricular coronary blood flow was normal in the patient with aortic stenosis. The left ventricular oxygen consumption per 100 grams per minute was normal in patients with aortic stenosis, with arteriovenous fistula, and with hyperthyroidism. It was elevated in the patient with aortic insufficiency.

In one patient with clinical and electrocardiographic evidence of coronary occlusion with myocardial damage, the left ventricular coronary flow per 100 grams per minute, the oxygen extraction, and the left ventricular oxygen consumption per 100 grams per minute were markedly reduced.

The results indicate that chronic increase in the energy requirements of the heart were met, not by an increase in the oxygen consumption per unit weight, but by an increase in the total oxygen consumption due to hypertrophy.

The efficiency of the failing heart was low as a result of markedly decreased work in conjunction with slightly increased oxygen consumption.

The cooperation of Dr. McGehee Harvey and Dr. Samuel Asper of the Department of Medicine, Johns Hopkins Hospital, is greatly appreciated.

REFERENCES

1. Kety, S. S., and Schmidt, C. F.: The Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations, *Am. J. Physiol.* **143**:53, 1945.
2. Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. M., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of Coronary Blood Flow by the Nitrous Oxide Method, *Am. J. Physiol.* **152**:356, 1948.
3. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. A.: Coronary Sinus Catheterization for Studying Coronary Blood Flow and Myocardial Metabolism, *Am. J. Physiol.* **152**:340, 1948.
4. Bing, R. J., Vandam, L. D., Gregoire, F., Handelsman, J. C., Goodale, W. T., and Eckenhoff, J. E.: Catheterization of the Coronary Sinus and Middle Cardiac Vein in Man, *Proc. Soc. Exper. Biol. & Med.* **66**:239, 1947.
5. Tandler, J. *Die Anatomie des Herzens*, Jena, G. Fischer, 1914.
6. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, *Proc. Soc. Exper. Biol. & Med.* **46**:462, 1941.
7. Moe, G. K., and Visscher, M. B.: The Mechanism of Failure in the Completely Isolated Mammalian Heart, *Am. J. Physiol.* **125**:461, 1939.
8. Gregg, D. E., and Shipley, R. E.: Studies on the Venous Drainage of the Heart, *Am. J. Physiol.* **151**:13, 1947.
9. Anrep, G. V., Blalock, A., and Hammouda, M.: The Distribution of Blood in the Coronary Blood Vessels, *J. Physiol.* **67**:87, 1928.
10. Macleod, J. J. R.: *Physiology and Biochemistry in Modern Medicine*, ed. 5, St. Louis, 1926, The C. V. Mosby Company, p. 780, Table V.
11. Powers, S. R., and Bing, R. J.: Unpublished observation.
12. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and the Weight of the Heart to Age, *AM. HEART J.* **41**:79, 1928.
13. Starling, E. H., and Evans, L. L.: The Respiratory Exchanges of the Heart in the Diabetic Animal, *J. Physiol.* **49**:67, 1914.
14. Evans, L. L., and Matsuoka, M.: The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, *J. Physiol.* **49**:379, 1914.
15. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61**:523, 1924.
16. Spencer, F. C., Powers, S. R., Merrill, D. L., and Bing, R. J.: Coronary Blood Flow and Cardiac Oxygen Consumption in Unanesthetized Dogs, *J. Clin. Investigation*. In press.
17. Green, H. D., and Gregg, D. E.: The Relationship Between Differential Pressure and Blood Flow in a Coronary Artery, *Am. J. Physiol.* **130**:97, 1940.
18. Eckenhoff, J. E., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of Hypotension on Coronary Blood Flow, Cardiac Work and Cardiac Efficiency, *Am. J. Physiol.* **152**:545, 1948.
19. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of Blood Pressure From the Left Auricle and the Pulmonary Veins in Human Subjects With Interauricular Septal Defect, *Am. J. Physiol.* **150**:267, 1947.
20. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, *J. Physiol.* **62**:243, 1926.
21. Katz, L. N., Wise, W., and Jochim, K.: The Control of the Coronary Flow in the Denervated Isolated Heart and Heart-Lung Preparation of the Dog, *Am. J. Physiol.* **143**:479, 1945.

THE ROLE OF DESICCATED THYROID AND POTASSIUM IODIDE IN THE CHOLESTEROL-INDUCED ATHEROSCLEROSIS OF THE CHICKEN

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EVER since Anitschkow¹ first succeeded in producing experimental arteriosclerosis in the rabbit, numerous attempts have been made to find some means of preventing or inhibiting the development of the cholesterol-induced lesions, or of causing the regression of the formed lesions. To date, the most encouraging progress in this direction has been with the use of the organic and inorganic iodides and of whole thyroid preparations. The voluminous and contradictory literature on the subject has recently been reviewed by Hueper.¹¹ There has been some hesitancy on the part of many observers to accept this work, all of which has been done in the rabbit, on the grounds that this animal is not a suitable experimental animal for work in arteriosclerosis. Their arguments have been summarized by Duff.¹⁰ In a search for a more suitable animal, Dauber and Katz¹² found that arteriosclerosis could be produced in the chicken by the feeding of a high-cholesterol diet. The atherosclerosis was characterized by intimal changes which resembled those seen in man. Furthermore, the chicken, unlike the rabbit, is an omnivore, and normally ingests considerable amounts of cholesterol in its diet. Perhaps of even greater importance is the fact that the chicken normally develops arteriosclerosis after the age of six months, and that by the age of one and one-half years more than 50 per cent of chickens show some evidence of this spontaneous type of arteriosclerosis.¹³ Because of the manifest advantages of this animal for studies of experimental atherosclerosis, we decided to employ it in our reinvestigation of the role of desiccated thyroid and potassium iodide in experimental cholesterol-induced atherosclerosis.

METHODS

Three separate series of experiments were run; the first between March and July, 1946 (Series one), the second between August and November, 1946 (Series two), and the third between August and November, 1947 (Series three). White Leghorn chicks between the ages of 5 and 7 weeks were used throughout.

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Aided by a grant from the Life Insurance Medical Research Fund.

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TABLE I. COMPOSITION OF THE EXPERIMENTAL GROUPS AND DIETS IN THE THREE SERIES

SERIES	SUBGROUP	NO. OF CHICKENS IN SUBGROUP	BASAL DIET	CHOLESTEROL ADDED (PER CENT)	DESICCATED THYROID	POTASSIUM IODIDE
One	Cholesterol controls	16	Chick starter mash	2	—	—
	Thyroid-Cholesterol	16	Chick starter mash	2	200 mg./kg./day	—
	Potassium iodide-Cholesterol	16	Chick starter mash	2	—	800 mg./kg./day
Two	Cholesterol controls	10	Chick starter mash	1	—	—
	Thyroid-Cholesterol	8	Chick starter mash	1	—	—
	Potassium iodide-Cholesterol	10	Chick starter mash	1	1.0 Gm./kg./day	2.0 Gm./kg./day
Three	Normal controls	10	Chick starter mash	—	—	—
	Cholesterol controls	10	Chick starter mash	1	—	—
	Thyroid-Cholesterol	10	Chick starter mash	0.5	—	—
	Thyroid-Cholesterol	20	Chick starter mash	1	700-800 mg./kg./day	—
	Potassium iodide-Cholesterol	20	Chick starter mash	0.5	700-800 mg./kg./day	—
	Potassium iodide-Cholesterol	20	Chick starter mash	1	—	1.4-1.5 Gm./kg./day
				0.5	—	1.4-1.5 Gm./kg./day

Male and female chicks were used in equal proportions in the first two series, and male chicks only were used in Series three. The compositions of the diets and the number of chickens in each group are shown in Table I. The base of the diet was chick starter mash obtained from commercial sources. Cholesterol was suspended in 20 per cent cottonseed oil and thoroughly mixed with the mash. In Series one and two, potassium iodide was dissolved in water and given two to three times a week by pipette, and in these two series desiccated thyroid was given in tablet form by mouth. In Series three, both the potassium iodide and the desiccated thyroid were mixed with the mash. The dosages of cholesterol employed were 2 per cent in Series one, 1 per cent in Series two, and 0.5 and 1 per cent in Series three. The dosages of desiccated thyroid were 200 mg. per kilogram per day in Series one, 1 Gm. per kilogram per day in Series two, and 700 to 800 mg. per kilogram per day in Series three. The dosages of potassium iodide were 800 mg. per kilogram per day in Series one and 2 Gm. per kilogram per day in Series two. In Series three, the dose was 1.4 to 1.5 Gm. per kilogram per day of potassium iodide.

Autopsies were performed on all animals, and careful gross and microscopic examinations were made. The heart and aorta of each animal were dissected out en bloc and carefully examined for atheromatous lesions. The lesions were fully described and sketched on prepared forms. They were graded for severity on an arbitrary scale of values from 0 to 4, depending on the severity of the lesions.¹⁹ The thoracic and abdominal portions of the aorta were graded separately, and the results were later combined as the total gross grading. Sections were also taken for microscopic examination. Total blood cholesterols were done at biweekly intervals by the method of Schoenheimer and Sperry.²⁰

RESULTS

The results have been tabulated on the basis of the total gross grading for the separate series and subgroups in Table II, and for all subgroups combined in Table III. For purposes of statistical analysis the data were rearranged in Table IV to demonstrate the effects obtained by thyroid and potassium iodide with different cholesterol loads. From this table it is apparent that at all concentrations of cholesterol, the chickens which received desiccated thyroid showed a lesser degree of atherosclerosis than did the control birds, which received only cholesterol. This effect was most marked in the group receiving 1 per cent cholesterol and thyroid (Series two), and least marked in the group receiving 2 per cent cholesterol and thyroid (Series one). The combined results for all the thyroid groups gave a chi square of 9.7, a value which is statistically significant. Reference to Table IV indicates that the results obtained with potassium iodide were equivocal. With cholesterol concentrations of 0.5 per cent and 2 per cent, the simultaneous feeding of potassium iodide appears, statistically, to aggravate the lesions. This did not hold true for the potassium iodide group of Series two, which received the highest dosage of the drug given and in which group the potassium iodide appeared, statistically, to have some effect in reducing the severity of the vascular lesions.

TABLE II. TOTAL GROSS GRADING OF ATHEROSCLEROTIC LESIONS OF THE AORTA IN INDIVIDUAL GROUPS (NUMBER IN EACH GROUP)

SERIES	GROUP	GRADE 0-1	GRADE 1½-3	GRADE 3½-8
One	2% Cholesterol controls	3	7	5
	2% Cholesterol-Potassium iodide	1	7	6
	2% Cholesterol-Thyroid	3	8	5
Two	1% Cholesterol controls	2	4	4
	1% Cholesterol-Potassium iodide	3	5	1
	1% Cholesterol-Thyroid	4	4	0
Three	Normal controls	10	0	0
	0.5% Cholesterol controls	7	3	0
	1% Cholesterol controls	3	6	0
	0.5% Cholesterol-Potassium iodide	6	10	4
	1% Cholesterol-Potassium iodide	8	5	2
	0.5% Cholesterol-Thyroid	10	1	0
	1% Cholesterol-Thyroid	4	5	0

Method of grading is that described previously¹⁹; since thoracic and abdominal lesions are added together the grades run from 0 to 8.

TABLE III. COMBINED GROSS GRADING OF ATHEROSCLEROTIC LESIONS OF THE AORTA IN ALL SERIES

GROUP	NUMBER WITH GRADE 0-1	PER CENT OF TOTAL IN GROUP	NUMBER WITH GRADE 1½-3	PER CENT OF TOTAL IN GROUP	NUMBER WITH GRADE 3½-8	PER CENT OF TOTAL IN GROUP
Cholesterol controls (0.5-1.2%)	15	33	20	45	9	22
Cholesterol-Thyroid	21	48	18	41	5	11
Cholesterol-Potassium iodide	18	31	27	47	13	22

Blood Cholesterol Levels.—The results for Series three are shown in Fig. 1, A and B, and are representative of those obtained in the two preceding series. In this series both the birds fed only 0.5 per cent and those fed 1 per cent cholesterol showed rapid and steady rises to high blood cholesterol levels. The groups which received potassium iodide and cholesterol showed blood cholesterol levels which were closely parallel to, but exceeded the levels for the birds fed cholesterol alone. The blood cholesterol values in the groups receiving thyroid and cholesterol were consistently about 50 per cent of those in the groups receiving cholesterol alone.

DISCUSSION

Liebig² demonstrated clearly that iodides would prevent the development of arteriosclerotic lesions in rabbits which were simultaneously receiving a high-cholesterol diet. This pioneer work has since been confirmed in the rabbit by many investigators. In 1927, Shapiro³ reported that thyroidectomized rabbits fed lanolin in cottonseed oil, in addition to their regular diet, were abnormally susceptible to the development of atherosclerotic lesions. Subsequent

TABLE IV. COMBINED GRADING OF ALL GROUPS ARRANGED ACCORDING TO CHOLESTEROL CONTENT OF DIET

	NUMBER WITH GRADE 0-1	NUMBER WITH GRADE 1½-8	PER CENT OF BIRDS WITH GRADING >1	CHI ² *	PROBA- BILITY† (PER CENT)
Cholesterol 0.5% Control Thyroid	7 10	3 1	30 9	0.44	
Cholesterol 1% Control Thyroid	5 14	14 5	73 26	8.5	<5
Cholesterol 2% Control Thyroid	3 3	12 5	80 63	0.83	
Total of three series				9.7	<5
Cholesterol 0.5% Control Potassium iodide	7 6	3 14	30 70	3.82	5
Cholesterol 1% Control Potassium iodide	5 11	14 13	73 54		
Cholesterol 2% Control Potassium iodide	3 1	12 13	80 93	0.22	

*Chi² test of independence statistically.†When *P* is less than 5 per cent, the difference is considered to be statistically significant.

reports from other investigators, namely, Turner and his associates,^{4,5,6} to the effect that desiccated thyroid would prevent the development of atherosclerosis and hypercholesterolemia, suggested that the thyroid gland might play a very important role in the pathogenesis of experimentally induced atherosclerosis in the rabbit. The nature of this role has been elucidated in large part through the studies of Turner and his associates. They showed that in the rabbit the thyroid exercises at all times a restraining influence on the blood cholesterol, strong enough to overcome the effect of the feeding of large amounts of cholesterol by mouth.⁵ The removal of the thyroid gland resulted in rising blood cholesterol levels in normal animals and in those receiving cholesterol either with high or normal blood cholesterol levels at the start, the last being the so-called "resistant" rabbits.⁵ They also discovered that the protective action of potassium iodide depended on the presence of the thyroid gland; and that potassium iodide failed to affect the blood cholesterol levels of the rabbit in the absence of the thyroid gland.⁷

Thyroid hormone, desiccated thyroid, and potassium iodide have all been shown to have striking effects on the levels of cholesterol in the blood.

Thyroid hormone and desiccated thyroid will prevent the blood cholesterol from rising to the high levels seen in cholesterol-fed animals, and will continue to exert this effect in the face of continued feeding of a high-cholesterol diet for many weeks.^{4,6} Potassium iodide will act only in the presence of the thyroid, as was demonstrated by Turner and Khayat,⁷ and then its effect in restraining the rise in blood cholesterol is only temporary.

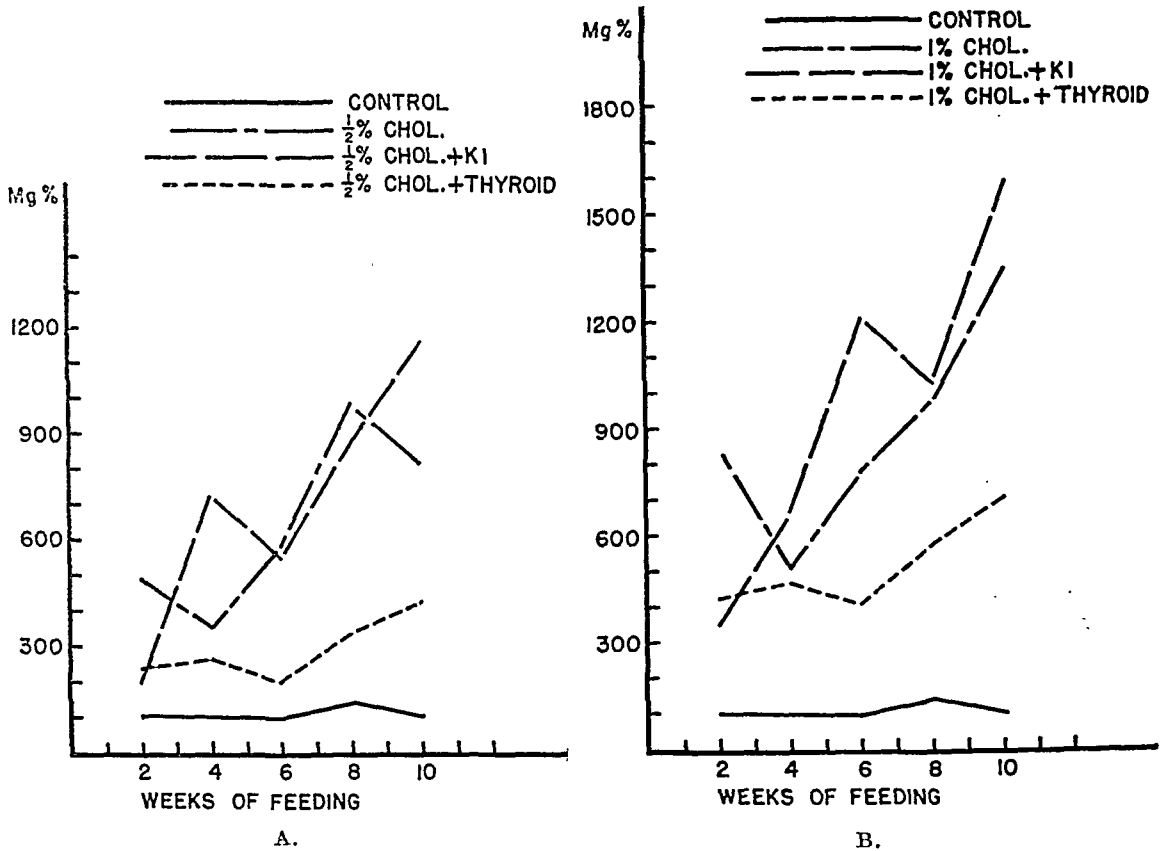


Fig. 1.—A and B, Blood cholesterol levels (total) Series three.

From these statements, it would appear that the effect of thyroid gland extracts in preventing arteriosclerosis is most likely through the action of these substances in restraining the blood lipids from rising to the high values seen in the control cholesterol-fed animals.

The picture, however, is not so simple as it seems. Although in most published reports there seems to be a close coincidence between the occurrence of atherosclerotic lesions and the levels of blood cholesterol, there are a number of reports which indicate that the protective action of potassium iodide and other iodides may not be entirely due to their effect on the blood cholesterol via the thyroid gland. Page and Bernhard⁸ found that the di-iodide of ricinoleic acid, when administered to rabbits simultaneously receiving a high-cholesterol diet, had no effect on the hypercholesterolemia and lipemia, although it exerted a protective effect on the vascular tissue. Ungar⁹ observed

the protective action of organic iodides in thyroidectomized animals, and Turner and Bidwell⁶ confirmed the protective action of potassium iodide on the thyroidectomized rabbit.

The mechanism of the protective effect of potassium iodide is not understood at present. It is known that iodides will combine in vitro with protein to form a biologically active substance which resembles thyroid hormone.¹⁶ It is also known that the function of the thyroid gland is (a) to selectively accumulate inorganic iodides and (b) to release elementary iodine for the formation of thyroid hormone.¹⁷ If free iodine is fed to a thyroidectomized animal, it can be utilized peripherally.¹⁸ There is proof that free iodine acts peripherally by forming a thyroid-hormonelike substance through combination with body proteins in areas other than the specialized tissues of the thyroid gland.¹⁸ The differences in the results obtained by various investigators are probably due to the presence or absence of free iodine in the iodide employed. In thyroidectomized animals, free iodine would act peripherally, while potassium iodide or other combined iodine would be ineffective.

Our results demonstrate clearly that when potassium iodide is given dissolved in water, with no free iodine present, it has no clear-cut protective effect on the degree of the atherosclerosis induced by simultaneous cholesterol feeding. With the lower dosage level of potassium iodide there even appears to be an aggravation of the severity of the cholesterol-induced lesions. It would appear, therefore, that the ability of the thyroid gland of the chick to produce thyroxin is not increased by its being presented with an abundance of inorganic iodide. Indeed, it would appear that under these conditions the ability of the thyroid to produce its hormone is impaired.

Our results confirm those of Turner and his associates,⁴ who found that desiccated thyroid substance, when fed in large doses together with cholesterol, is protective to a considerable extent against the development of atherosclerosis in the rabbit. We have observed only a partial and statistical degree of protection, which depended in large part on the relative doses of cholesterol and thyroid administered. This is in contrast to the almost complete protection observed by Turner and others⁴ in the rabbit. Again, in contradiction of Turner,⁴ we have been unable to observe any protective action of potassium iodide in the chicken. The recent work of Dvoskin,¹⁸ which showed the ability of the peripheral tissues to utilize free iodine for the formation of thyroxin-like material, would suggest that the role of iodine must be re-evaluated, both in the rabbit and in the chicken, by this newer method.

The behavior of the blood cholesterol under the conditions imposed was identical with that reported by Turner^{4,6} as far as the effect of thyroid was concerned. Whereas Turner observed a temporary effect of potassium iodide in restraining the blood cholesterol rise due to the feeding of cholesterol, no such phenomenon was observed in our series. Instead, the potassium iodide caused a rise of the blood cholesterol values above normal, and this effect was maintained throughout the course of the experiment. At present, it is not possible to say whether the effect of thyroid substance in protecting the vascular tissues

against the development of atherosclerosis is due simply to its action in inhibiting the rise in blood cholesterol which occurs when cholesterol is fed, or whether thyroid substance also possesses some specific effect on the vascular tissues. The work of Fleischmann and Shumacker¹⁴ indicates that thyroxin causes a shift of cholesterol from the blood to the tissues without affecting the total amount of cholesterol in the body. Hueper¹¹ has suggested that the instability of the lipid-protein complex in the blood leads to the deposition of lipids in the arterial intima, and that the protective action of thyroid hormone lies in "stabilizing" the lipid-protein complex of the blood.

Finally, the amount of desiccated thyroid given was very large, in the neighborhood of 0.8 to 1.0 Gm. per kilogram per day, which represents the upper limit of tolerance of the chicken for this drug. Herrmann¹⁵ and others have used desiccated thyroid and potassium iodide in clinical trials and reported some effect. It is difficult to evaluate the effect of the drugs in clinical material, and it would seem by inference from the animal work that the doses of thyroid required would be unsafe for clinical use.

SUMMARY

1. Chickens were fed desiccated thyroid and potassium iodide, together with cholesterol, in varying concentrations, in an attempt to determine the effect, if any, of these substances on cholesterol-induced atherosclerosis.

2. Potassium iodide in doses ranging from 800 mg. per kilogram per day to 2,000 mg. per kilogram per day gave equivocal results. With a dose of 2,000 mg. per kilogram per day in animals receiving 1 per cent cholesterol, some protective action was observed. In chickens receiving 0.5, 1, and 2 per cent cholesterol and smaller doses of potassium iodide, the drug appeared to aggravate the severity of the lesions.

3. Desiccated thyroid in doses of from 200 mg. per kilogram per day to 1,000 mg. per kilogram per day gave consistent results. Some degree of protection was seen in all series. The degree of protection depended on the relative doses of thyroid and cholesterol given.

4. Desiccated thyroid minimized the rise in the blood cholesterol levels seen in the cholesterol-fed control chickens. This inhibitor effect of desiccated thyroid on the blood cholesterol was maintained throughout the course of the experiment. In potassium iodide-treated chickens the blood cholesterol levels were higher than in the cholesterol-fed control chickens.

We wish to thank the other members of the Cardiovascular Department for their valuable assistance in the conduct of these experiments, and Mr. Herbert Silverstone of the Department of Cancer Research for his statistical treatment of the material.

REFERENCES

1. Anitschkow, N.: Ueber Veränderung der Kanischen-Aorta bei experimenteller Cholesterinsteatose, *Beitr. z. path. Anat. u. z. allg. Path.* 56:379, 1913.
2. Liebig, H.: Die Beeinflussung der experimenteller Atherosklerose durch Jodbehandlung, *Arch. f. exper. Path. u. Pharmacol.* 159:265, 1931.
3. Shapiro, S.: The Relation of Certain Glands of Internal Secretion to the Development of Atherosclerosis, *Endocrinology* 11:279, 1927.
4. Turner, K. B.: Studies on the Prevention of Cholesterol Induced Atherosclerosis in Rabbits. I. The Effects of Whole Thyroid and Potassium Iodide, *J. Exper. Med.* 58:115, 1933.
5. Turner, K. B., Present, C. H., and Bidwell, E. H.: The Role of the Thyroid in the Regulation of the Blood Cholesterol of Rabbits, *J. Exper. Med.* 67:111, 1938.
6. Turner, K. B., and Bidwell, E. H.: Further Observations on the Blood Cholesterol of Rabbits in Relation to Atherosclerosis, *J. Exper. Med.* 62:721, 1935.
7. Turner, K. B., and Khayat, G. B.: Influence of Thyroidectomy on Protective Action of Potassium Iodide, *J. Exper. Med.* 58:127, 1933.
8. Page, I. H., and Bernhard, W. G.: Cholesterol Induced Atherosclerosis. Its Prevention in Rabbits by Feeding an Organic Iodine Compound, *Arch. Path.* 19:530, 1935.
9. Ungar, H.: Zur Wirkung des Jods auf die Cholesterin-Atheromatose der Kaninchen, *Arch. f. exper. Path. u. Pharmacol.* 175:536, 1934.
10. Duff, G. L.: Experimental Cholesterol Arterio-sclerosis and Its Relationship to Human Arteriosclerosis, *Arch. Path.* 20:81, 1935.
11. Hueper, W. C.: Arteriosclerosis, *Arch. Path.* 38:162, 1944.
12. Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick, *Arch. Path.* 34:937, 1942.
13. Dauber, D. V.: Spontaneous Arterio-sclerosis in Chickens, *Arch. Path.* 38:46, 1944.
14. Fleischmann, W., and Shumacker, H. B., Jr.: Cholesterol and Thyroid Function, *Bull. Johns Hopkins Hosp.* 71:175, 1942.
15. Herrmann, G. R.: Some Experimental Studies in Hypercholesterolemic States, *Exper. Med. & Surg.* 5:149, 1947.
16. Reineke, E. P.: Thyroactive Iodinated Proteins, Vitamins and Hormones 4:207, 1946.
17. Harrington, C. R.: Newer Knowledge of the Biochemistry of the Thyroid Gland, *J. Chem. Soc. London* 1:193, 1944.
18. Dvoskin, S.: The Thyroxin-like Action of Elemental Iodine in the Rat and Chick, *Endocrinology* 40:334, 1947.
19. Horlick, L., and Katz, L. N.: The Relationship of Atheromatosis Development in the Chicken to the Amount of Cholesterol Added to the Diet, *AM. HEART J.* In press.
20. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, *J. Biol. Chem.* 106:745, 1934.

PRODUCTION OF ARTERIOSCLEROSIS IN DOGS BY CHOLESTEROL AND THIOURACIL FEEDING

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PROGRESS in the study of arteriosclerosis is largely dependent on the reproduction of the disease in animals because this pathologic condition cannot be adequately diagnosed and followed clinically. Until recently, the experimental arterial lesions that most closely resembled human arteriosclerosis occurred in rabbits, following an elevation of blood cholesterol as a result of a high-cholesterol diet.¹ Numerous attempts^{2,3,4} to produce arteriosclerosis in other species have been unsuccessful except in the chicken.⁵ Although the arteriosclerosis in rabbits is similar in many respects to that which occurs in man, Duff⁶ and other investigators⁷ have emphasized three important objections: (1) The distribution of the lesions in rabbits differs from that occurring in man in that the lesions are most extensive in the abdominal aorta and its branches. In addition, cerebral and renal arteriosclerosis does not occur in rabbits. (2) The morphologic appearance of the lesions in rabbits resembles that seen in the early stages of arteriosclerosis in man, but the more advanced type of lesion does not develop. (3) The feeding of cholesterol fails to result in a significant hypercholesterolemia and arterial lesions in omnivorous mammals, such as the dog, rat, cat, or monkey, whose diet normally contains cholesterol.

However, in a recent study from this laboratory,⁸ it was demonstrated that arterial lesions in dogs, similar in distribution and microscopic appearance to human arteriosclerosis, resulted from prolonged hypercholesterolemia.

The present communication records further studies confirming and extending the original report.

METHOD

Seven mongrel dogs, 3½ months old at the onset of the experiment, were used. After an initial control period of one to two weeks, the animals were divided into three groups. Group A, consisting of three animals (No. 428, No. 429, and No. 430), was fed 1.0 Gm. of thiouracil* daily together with the regular diet

This investigation has been aided by a grant from the United States Public Health Service and from the Albert and Mary Lasker Foundation.

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Presented at the Twenty-first Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

*Thiouracil was kindly supplied for this investigation by Dr. S. M. Hardy of Lederle Laboratories.

(Spratt's meat fibrine dog cakes) for fourteen to fifteen months. Group B, consisting of two dogs (No. 2951 and No. 2947), was fed 10 Gm. of crystalline cholesterol daily together with the regular dog food for sixteen months. The cholesterol was dissolved in ether, mixed through the dog food, and the ether then allowed to evaporate. Group C, consisting of two dogs (No. 2935 and No. 2934), were fed increasing amounts of thiouracil daily, 0.8 Gm., for the first two months, 1.0 Gm. for the third month, and 1.2 Gm. from the fourth through the twelfth month, plus 10 Gm. of cholesterol added to the regular diet. Serum cholesterol determinations, using the method of Schoenheimer and Sperry,⁹ were made biweekly during the course of the study. All of the animals remained in good general health and gained weight during the experiment.

The animals were sacrificed at the end of the study by exsanguination under phenobarbital sodium anesthesia. Post-mortem examinations were made in each instance.

TABLE I. SERUM CHOLESTEROL VALUES IN DOGS (MG. PER 100 CUBIC CENTIMETERS)

<i>Group A</i>						
DOG NUMBER	CONTROL PERIOD			THIOURACIL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
428		225	1	309-530	408	14
429		322	1	307-594	415	15
430		131	1	176-490	359	14

<i>Group B</i>						
DOG NUMBER	CONTROL PERIOD			CHOLESTEROL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
2947	178-180	179	2	294-736	449	16
2951	111-150	130	2	212-624	408	16

<i>Group C</i>									
DOG NUMBER	CONTROL PERIOD			CHOLESTEROL PERIOD			CHOLESTEROL AND THIOURACIL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
2935	144-147	145	2	400-565	447	1	505-2350	1206	12
2934	79-178	128	2	344-418	388	1	570-1617	1089	12

RESULTS

Serum Cholesterol Determinations.—The serum cholesterol levels of the three animals in Group A on thiouracil alone averaged 408 mg. per cent, 415 mg. per cent, and 359 mg. per cent, respectively, during the thiouracil period of fourteen to fifteen months (Table I).

The serum cholesterol levels of the two dogs on the high-cholesterol program (Group B) for sixteen months averaged 449 and 408 mg. per cent, respectively, during the course of the feeding. This represented an average increase of 270 and 278 mg. per cent, respectively, over the control values (Fig. 1).

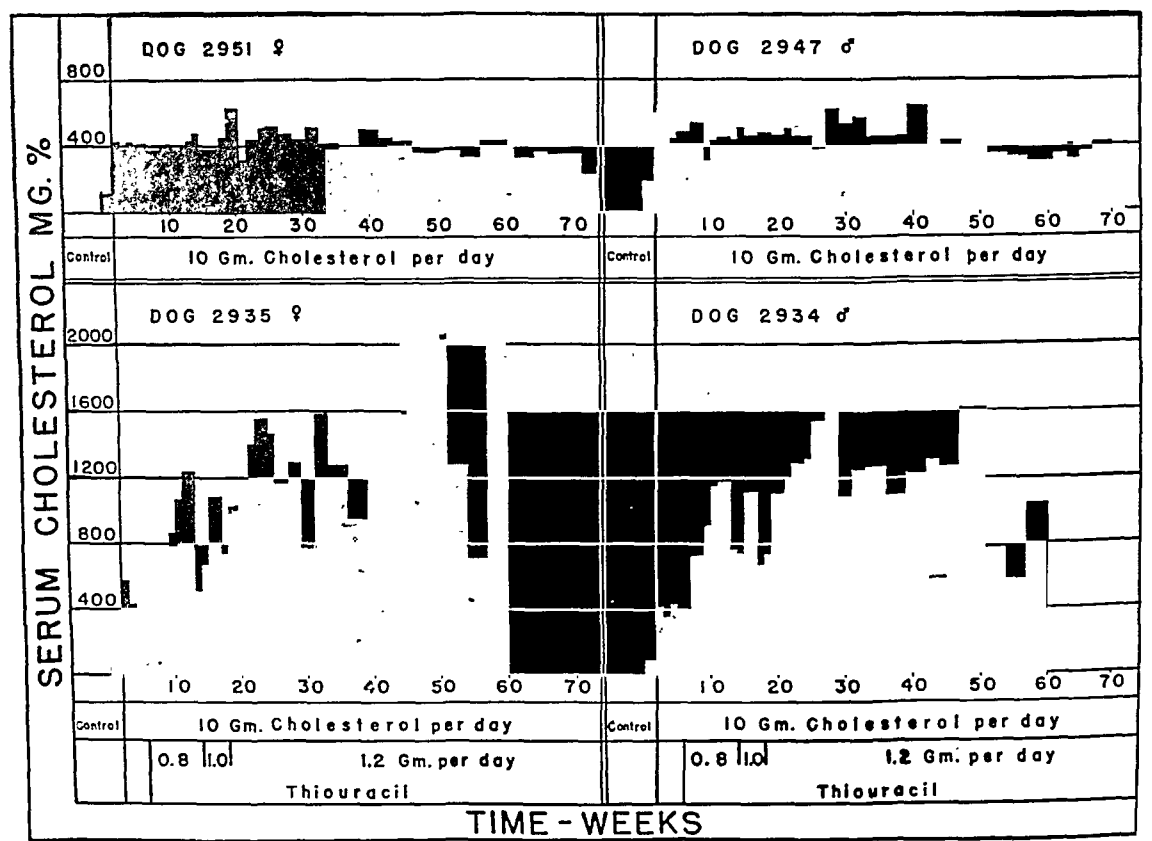


Fig. 1.—Levels of total serum cholesterol, as determined at weekly intervals during preliminary control period and during periods of cholesterol feeding in Dogs 2951 and 2947, and during cholesterol plus thiouracil feeding in Dogs 2935 and 2934.

The dogs on the high-cholesterol diet and thiouracil (Group C) had average serum cholesterol levels of 1,206 and 1,089 mg. per cent, respectively, during the twelve months of the experiment. This represented an average increase of 1,061 mg. and 961 mg., respectively, over control levels (Fig. 1).

Arterial Lesions.—A complete necropsy was performed on all animals immediately after sacrifice. All organs as well as the aorta and its major branches were examined microscopically. The three dogs on thiouracil for fourteen to fifteen months were completely free of arterial lesions.

One of the two dogs on the high-cholesterol diet had a few fine, raised, yellow streaks in the abdominal aorta. On microscopic section, these were seen to consist of lipid depositions in the aortic intima, forming an early arteriosclerotic lesion. The second dog on the high-cholesterol diet had no arterial lesions.



Fig. 2.—Abdominal aorta showing multiple intimal arteriosclerotic plaques which coalesce about exit of branches. The circular muscle bundles of the iliac arteries are accentuated by the plaques.

Post-mortem examination of the two dogs on the cholesterol plus thiouracil regime revealed extensive generalized arteriosclerosis. The lesions varied in size from small, pin-point, yellowish elevations of the intima to large coalescing plaques. The lesions were most marked in the abdominal aorta and its branches. The coronary arteries were diffusely involved, with resulting narrowing of the lumen of the vessels. Gross lesions were present on the anterior leaflet of the mitral valve as well as in the sinuses of Valsalva. The arteries forming the circle

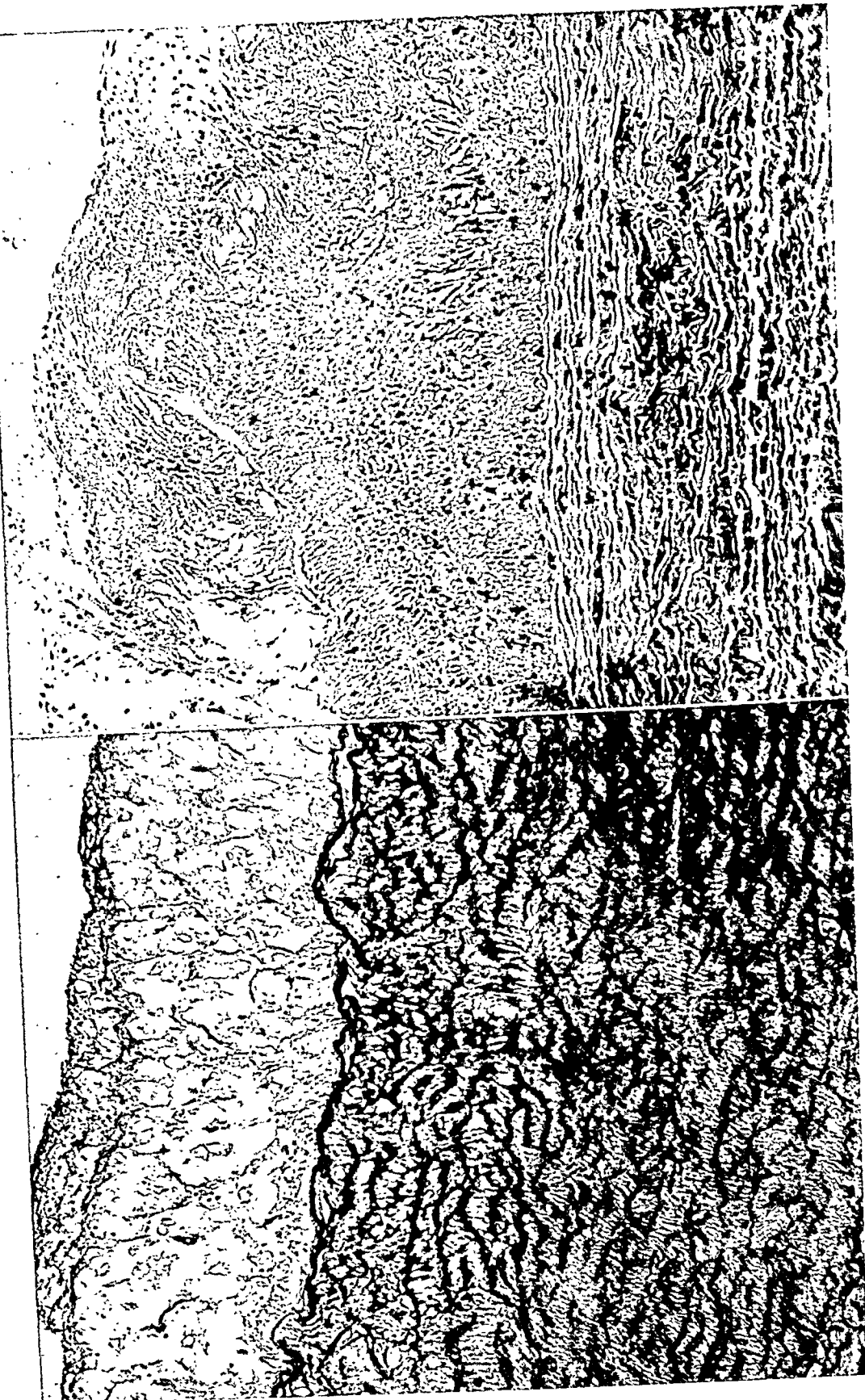


Fig. 3.

Fig. 3.—Thoracic aorta. An early arteriosclerotic lesion showing a thickening of the intima by lipid infiltration with the internal elastica intact. Lipid has also infiltrated to the media, giving it a loose vacuolated appearance. Elastic tissue stain $\times 163$.

Fig. 4.

Fig. 4.—Iliac artery. An advanced arteriosclerotic plaque with foam cells and fibrosis. Vacuolated spaces representing lipid appear in the internal elastica. The internal elastica is visible at the left but disappears beneath the fibrotic area of the plaque. Hematoxylin and eosin stain, $\times 163$.

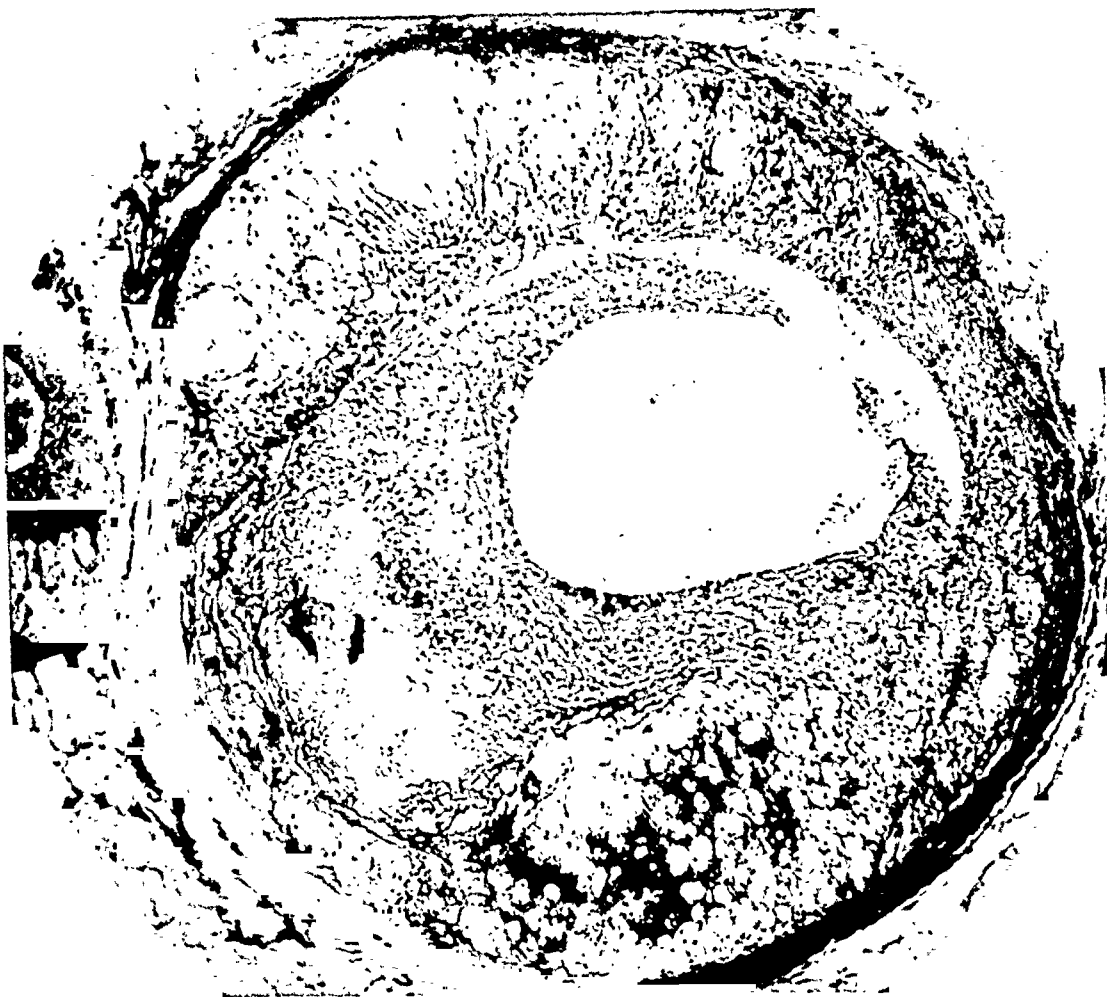


Fig. 5.—Coronary artery showing advanced arteriosclerosis with many of the sequelae of human arteriosclerosis. The lumen is narrowed by diffuse atheromatous deposits. Within the plaque are hemorrhage, hyalinization, and calcium. The media has been partially replaced by lipid deposits. Hematoxylin and eosin stain, $\times 86$.

of Willis contained numerous yellow atheromatous plaques. In addition, gross plaques were present in the thoracic aorta, thyroid, subclavian, innominate, iliac, femoral, mesenteric, and renal arteries.

Microscopic examination of the lesions described (Figs. 2-6) showed all stages of development seen in human arteriosclerotic plaques. Infiltration of the intima with foam cells and proliferation of the intima were present in the early stages. In older lesions, a layer of fibrous tissue, which was partially hyalinized, covered and depressed the lipid-containing foam cells deep into the plaque. Hemorrhage and calcification occurred within the plaques of the coronary arteries. Varying amounts of lipid could be demonstrated within the media of the arteries beneath the intimal plaques.

The only other findings of note were the hyperplasia of the thyroid gland and the presence of large amounts of fat in the liver, spleen, and kidneys comparable to that described in the original experiment.⁸

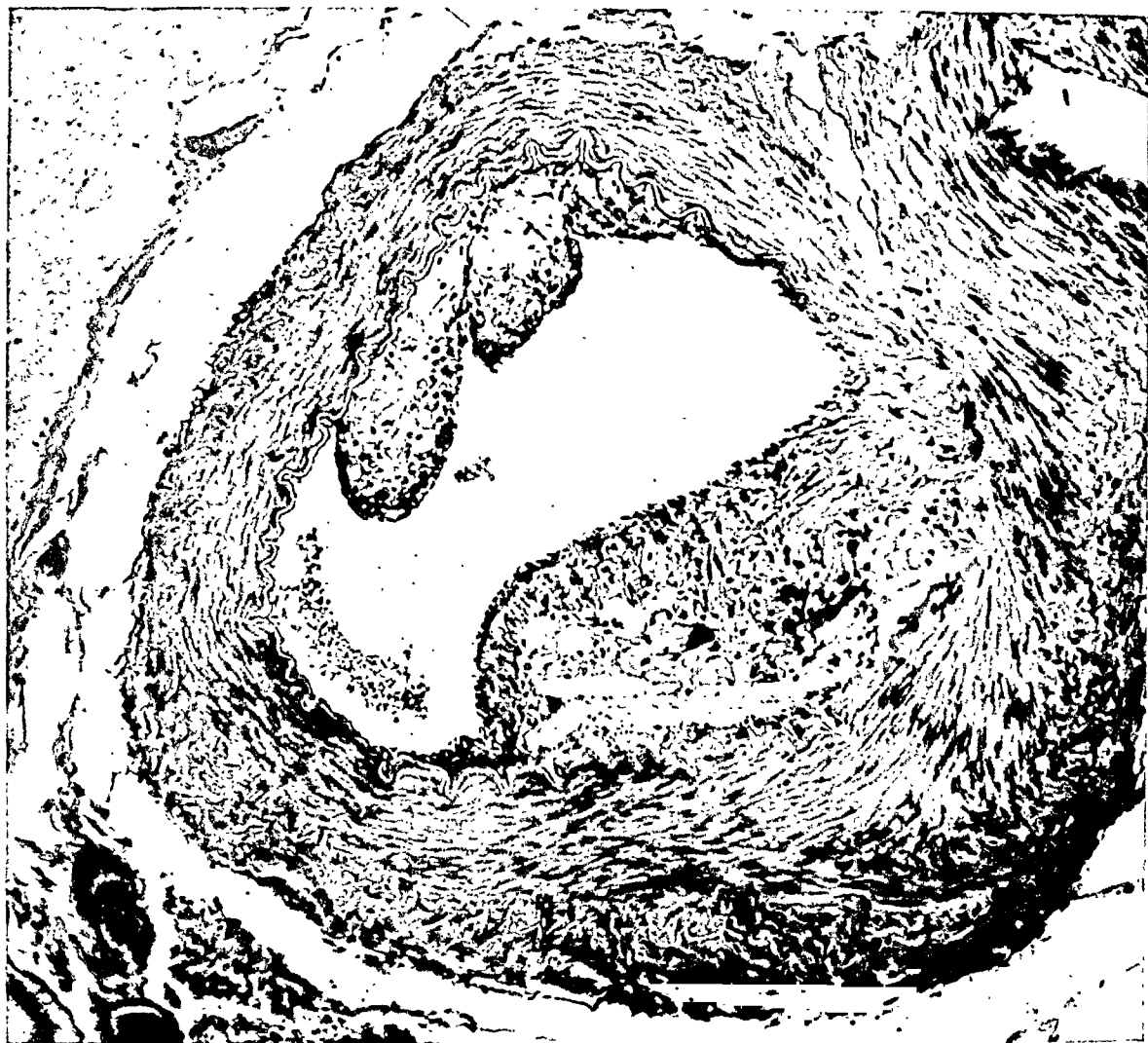


Fig. 6.—Middle cerebral artery. Initial atheromatous deposits narrow the lumen. Fibrous tissue beneath the endothelium and at the edges of the larger plaque is encroaching upon the foam cells. Hematoxylin and eosin, $\times 144$.

DISCUSSION

The present report confirms and extends a previous study from this laboratory in that extensive and generalized arteriosclerosis has been produced in young dogs by the feeding of cholesterol and thiouracil for one year. In addition, the feeding of cholesterol for sixteen months without thiouracil has been shown to result in the production of early arteriosclerotic plaques in the abdominal aorta of one of the two young dogs. The feeding of thiouracil without cholesterol to three animals for fifteen months failed to cause arterial lesions.

The present study differs from the earlier one in two respects: First, the animals in this experiment were $3\frac{1}{2}$ months old at the onset while the exact ages of the animals in the initial report were not known. Second, in the previous study, the cholesterol was suspended in 40 c.c. of cottonseed oil and then mixed through the dog food, whereas in the present experiment, no added fat was

used; the cholesterol was dissolved in ether and mixed through the dog food, and the ether was then allowed to evaporate.

The degree and extent of arteriosclerosis in the dogs that have been studied to date bears a direct relationship to the duration and elevation of the serum cholesterol. The average cholesterol level must exceed 450 mg. for more than one year before arteriosclerotic lesions are evident. It might be possible to produce arteriosclerosis in a shorter period of time if higher serum cholesterol levels are maintained.

In addition to the production of arteriosclerosis of the aorta and its branches, cerebral arteriosclerosis has occurred in the animals on the high-cholesterol and thiouracil program. Previous attempts to produce experimental arteriosclerosis of cerebral vessels have been unsuccessful, even in the rabbit.¹⁰ This difference between experimental arteriosclerosis and human arteriosclerosis has formerly been cited as one of the objections to transferring the results of experimental studies in animals to man. The distribution of the arteriosclerosis in the aorta of the dog is similar to that occurring in man in that the lesions are most marked in the abdominal aorta and its branches while in the rabbit the lesions are most prominent in the ascending aorta and the arch of the aorta. Thus, the experimental arteriosclerosis as produced in the dog is analogous to that in man so far as the site of occurrence of the lesions is concerned.

In the microscopic sections it can be seen that all stages from early to advanced forms of arteriosclerosis occurred in the dogs. The lesions of the coronary arteries, in particular, are almost identical with the human variety in that narrowing of the lumen was produced by thickening of the arteries, fibrosis, calcification, and hemorrhage into the wall of the arteriosclerotic plaque. The experimental arteriosclerosis in dogs is comparable to that occurring in man, whereas in the rabbit only the early stages of the arteriosclerotic process are seen microscopically.

The objections that have been raised to bring out the disparity between the experimental arteriosclerosis in the rabbit and that which occurs in man are probably the result of species differences and may not represent a fundamental difference in the pathogenesis of the disease process. Certainly the studies in this report indicate that experimental arteriosclerosis, which closely resembles human arteriosclerosis, can be produced in the dog, an omnivorous mammal.

Now that an acceptable laboratory tool is available, methods of preventing or curing arteriosclerosis are under study. Lipotropic substances which have been found to be effective in preventing or curing experimental arteriosclerosis in the rabbit^{11,12} are being investigated in the dog.

SUMMARY

1. The production of arteriosclerosis in an omnivorous mammal, the dog, by the feeding of cholesterol and thiouracil has been confirmed.
2. The resultant arteriosclerotic lesions in the dog have the same anatomical distribution and sites of predilection as do lesions in man, including the occurrence of cerebral arteriosclerosis.

3. The morphological features of the arteriosclerotic lesions in dogs resemble those of human arteriosclerosis in that infiltration of the intima with foam cells and proliferation of the endothelium of the intima occurs in the early lesions, while extension into the media, hyalinization, hemorrhage, and calcification develop in the more advanced plaques.

4. It has been demonstrated that thiouracil in the dosage used does not lead to arterial lesions.

5. The feeding of 10 Gm. of cholesterol daily, in addition to the regular diet, containing less than 5.0 per cent fat, without thiouracil, resulted in a moderate hypercholesterolemia and early arteriosclerosis in one dog.

REFERENCES

1. Anitschkow, N.: Ueber Veränderungen der Kaninchen Aorta bei experimenteller cholesterinsteatose, *Beitr. z. path. Anat. u. z. allg. Path.* **56**:379, 1913.
2. Anitschkow, N.: Einige Ergebnisse der experimenteller Atheroskleroseforschung, *Verhandl. d. deutsch. path. Gesellsch.* **20**:149, 1925.
3. Pfeleiderer, E.: Tierexperimentelle Untersuchungen über Arteriosklerose unter besondere Berücksichtigung der Krantzarteriensklerose, *Virchows Arch. f. path. Anat.* **284**:154, 1932.
4. Kawamura, R.: Neue Beiträge zur Morphologie der Cholesterinsteatose, Jena, 1927, G. Fischer.
5. Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in Omniverous Animal, the Chick, *Arch. Path.* **34**:937, 1942.
6. Duff, G. L.: Experimental Cholesterol Arteriosclerosis, and Its Relationship to Human Arteriosclerosis, *Arch. Path.* **20**:81, 259, 1935.
7. Aschoff, L.: Eindrücker von der Hundred-Jahnfeier der British Medical Association, München. *med. Wchnschr.* **79**:1403, 1932.
8. Steiner, A., and Kendall, F. E.: Atherosclerosis and Arteriosclerosis in Dogs Following Ingestion of Cholesterol and Thiouracil, *Arch. Path.* **42**:433, 1946.
9. Schoneheimer, R., and Sperry, W. M.: Micromethod for Determination of Free and Combined Cholesterol, *J. Biol. Chem.* **106**:745, 1934.
10. Pollak, O. J.: Attempts to Produce Cerebral Atherosclerosis, *Arch. Path.* **39**:16, 1945.
11. Steiner, A.: Effect of Choline in the Prevention of Experimental Aortic Atherosclerosis, *Arch. Path.* **45**:327, 1948.
12. Steiner, A.: Action of Choline on Experimental Aortic Atherosclerosis, *Proc. Soc. Exper. Biol. & Med.* **39**:411, 1938.

SURGICAL TREATMENT OF ANEURYSMS

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THE purpose of this paper is twofold. It is, first, to describe our results in operating 218 times on 177 patients who had arterial or arteriovenous aneurysms, and second, to bring to attention a group of patients who have unrecognized arteriovenous connections we call arterial varices.

The possible control of aneurysms has been a challenge to surgeons from the earliest days and surgical history is replete with the attempts in this direction of the most skillful surgeons in this field. Kocher, Miculicz, John Hunter, Halstead, and more recently Matas, Carrel, Reid, Babcock, Holman, and Elkin compose but a partial list of those who tried to control aneurysms. In general, there are two types of aneurysms: those involving the arterial tree only and those in which both the arteries and veins are connected. Either type may result from congenital or developmental failure, from trauma, or from degeneration of vessels due to disease.

Congenital arterial defects are rare, but arteriovenous aneurysms, other than those due to trauma, are, in the main, of a congenital nature. These connections normally present in fetal life sometimes do not close, and in this category can be placed many of the hemangiomas, the port-wine blemishes, and other vascular anomalies, some of which develop into aneurysms as time goes on. Certain of these congenital arteriovenous aneurysms continue to spread despite all types of therapy and they well may be called the carcinoma of the vascular system. They do not kill by metastasizing as do cancers, but they may destroy by locally spreading, always being ahead of efforts of therapy and eventually causing hemorrhage and death. One hundred fourteen of our patients had this congenital type of lesion.

The most common type of trauma is gunshot or stab wounds as seen during the war, but, with the increasing speed of locomotion, more result from airplane or automobile accidents. Twenty-four aneurysms of this type are here reported.

With the longevity which has followed the progress of medicine, more patients are reaching the age at which certain diseases, still unconquered, so weaken the blood vessel walls that aneurysmal dilatations follow. The span

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Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

of life has increased by one-third in the last one hundred years with twice as many people 65 or older alive today as then. Should this same rate be continued, that figure will be doubled again before the end of the century.¹ While our control of certain diseases has been phenomenal, our handling of complications of old age and disease occurring late in life has not kept pace. One example is arteriosclerosis, which is present in 40 per cent of all persons over 40 years of age,² with its complications, one of which is aneurysm, developing as the arterial wall degenerates. We include thirty-nine patients in this category.

The symptoms of aneurysm vary with the type, site, duration, and extent of the lesion, and time will not be taken to describe them or the effect of these lesions on the heart and circulation, since they are well known.

In the arterial aneurysm, with the disintegration of the vessel, the wall, and especially the media, dilates and/or ruptures. The inability of any structure, including bone, to stand against these aneurysms is definite. Occasionally, clot may form in an aneurysm and produce spontaneous closure, but this outcome is the exception. In general arterial aneurysms increase in size until rupture or embolism occurs. In the arteriovenous aneurysms, especially the congenital ones, so many vessels are encountered which are of such immature nature that the operation is frequently like putting a scalpel into a wet sponge. Pressure is required for control and these blood spaces, sometimes lined by only a single endothelial layer of cells, tear readily when a clamp is applied and are ligated with the greatest difficulty.

TREATMENT OF ARTERIAL ANEURYSMS

I. *Excision With End-to-End Anastomosis*.—This procedure is the ideal treatment in arterial aneurysms. This is possible in nearly all small traumatic aneurysms and in some others. A radial aneurysm in a boy of 4 years is an example. Occlusion of the radial artery was followed by blanching and evident loss of circulation in the thumb and first two fingers. End-to-end anastomosis even in a vessel this small was accomplished readily with fine silk by rerouting the vessel and flexing the wrist. The hydrodynamic law that pressure at any point in the vessel wall is inversely proportional to the rate of flow helps in making an anastomosis, since the rate of flow is rapid in arteries and wall pressure is therefore low.

II. *Venous Transplant*.—In these patients in whom the aneurysm results in a large arterial defect and when life of the part depends on the arterial continuity, a vein may be used as a transplant. This may be sutured into place. We have used it on four occasions. The use of a tube lined by a vein as advocated originally by Crile³ and Landon⁴ and lately by Blakemore and Lord,⁵ is a continuation of this principle. While this tube may occasionally be life saving, rupture has occurred at the tube end; in our experience suture technique is more satisfactory. Blalock²² and Murray²³ likewise favor suturing.

III. *Obliteration Operation*.—The Matas operation¹⁷ now has had fifty years of trial and where anastomosis is impossible it is the operation of choice, as it does not destroy the collateral circulation developed around the sac. To

this operation we have added the implant of a large contiguous muscle placed directly in the sac. This supplies a core, obliterates the space, and the sac^{7,8} is closed over it. We have had no recurrence in this type of procedure and it now has been performed on twenty-eight patients.

IV. *Occlusion by Proximal Ligation.*—In larger arteriosclerotic aortic aneurysms, hopeless without therapy, efforts to obliterate the aorta by ligation have continued. Biggers,⁹ Matas,¹⁰ and Elkin¹¹ each have reported success. We have obliterated the abdominal aorta for aneurysm by ligation below the renal arteries transperitoneally in five instances. In the first four of these we ligated with two cotton tapes in hour glass fashion to avoid too great pressure at one point. In three of these four, rupture followed in from six to eighteen months, the rupture occurring at the site of the proximal tape. In each, the signs of aneurysm disappeared and at autopsy in two the sac was found to be completely clotted, and in the other, partially thrombosed. The other patient has not ruptured in one year and may be cured. It was apparent that abdominal aneurysm could be cured if the technical difficulty of erosion at the ligation site could be solved. Following the work of Reid,¹² we then made an incision in the aorta between two cotton tapes, the distal one tied, and inserted a piece of fascia, with one end protruding, and then tied the proximal tape. A fascial plug proximal to the cotton tape was then present to take the shock of the obliteration. This patient has now survived nearly one year (Fig. 1).

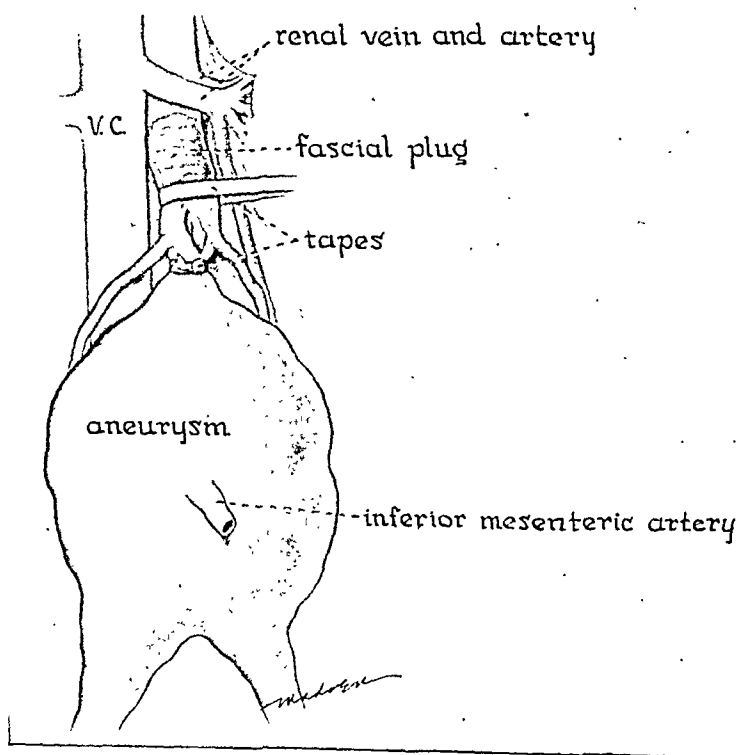


Fig. 1.—Ligation of abdominal aorta for aneurysm after insertion of fascial plug. Fascia placed to take shock of occlusion from the point of ligation and reduce possibility of rupture.

V. *End-to-End Artery-Vein Anastomoses Distal to Aneurysm* (Babcock²¹).—This operation decreases the wall pressure of the aneurysm by increasing the rate of flow, the blood returning directly to the heart instead of going to the periphery. This method has been used in six thoracic aneurysms and one iliac aneurysm. All but one were done in conjunction with Dr. Babcock.

VI. *Extra-arterial Irritation With Obliteration*.—The fact that an irritant around an aorta will cause sufficient reaction to obliterate it has been known since the work on dogs by Poppe and his associates.¹⁴ Cellophane was used initially and we added talcum powder, another tissue irritant. Experimentally, this produced the ideal slow occlusion, but in diseased vessels the results are not as satisfactory. We have used it six times. One patient whose aneurysm is in the ascending aorta is well after seven years. In another patient with an aneurysm in the innominate artery, operation was followed by a fatal mediastinitis. In one patient with an aneurysm in the aorta at the diaphragm level, operation caused the bruit to disappear for a year. Later, rupture into the thorax occurred and the autopsy showed an arteriovenous aneurysm also present. The possibility of the Cellophane irritating other vessels must be considered in this case. The other three patients are alive and apparently well.

VII. *Wiring and Coagulation*.—This method, introduced for the treatment of syphilitic aneurysms, is not within the scope of this paper. Blakemore¹⁵ has continued the work of Moore and Corradi¹⁶ and has reported encouraging results. Nearly all surgeons have abandoned this type of treatment. After all operations for arterial aneurysms on an extremity, temporary or permanent sympathectomy is advocated.

Comment.—One patient had a grapefruit-sized false arterial aneurysm of the left subclavian artery, extending from the aorta to the axilla. In operating on this patient control proximal to the aneurysm was difficult to obtain. When a tape was passed around the subclavian artery at its origin, the mass, as a result of its degeneration, broke from the aorta. Hemorrhage which can only be described as "terrific" occurred. Such a hemorrhage from the aorta will exsanguinate a patient within five seconds. The operator's hand was placed immediately in the opening and, with his fingers directly in the aorta, the external bleeding was temporarily controlled. The aneurysmal sac then was openly incised, all clots were evacuated, and the laminated layers removed until the point of rupture of the subclavian aneurysm was revealed. The entire pectoralis major muscle was then mobilized, divided at its insertion on the humerus, and then placed in the opening as the fingers were withdrawn. Efforts were made to place the muscle against but not into the aorta. Two leg rolls, covered with oxidized cellulose were then packed around the area. The muscle was held in place by suturing of the subcutaneous and cutaneous structures over it and the hemorrhage was controlled. Considering this but a temporary expedient, the patient was reoperated one week later and when the wound had been opened it was found that the muscle was well adherent to the aorta, there was granulation about it, and no hemorrhage occurred when the packing was removed. The sac was then obliterated. This case is mentioned because of the

tendency in such an emergency to consider hemorrhage uncontrollable. It emphasized again that pressure in such events is the best method to control bleeding as clamping would have caused further laceration of the vessel. It emphasized also that the best instruments so far devised for the emergency control of hemorrhage are the operator's hands. This patient was alive one year after this emergency.

TREATMENT OF ARTERIOVENOUS ANEURYSM

I. *Excision and End-to-End Anastomoses.*—In small aneurysms of this type this procedure is preferred, especially in end arteries.

II. *Repair of Artery.*—This may be done through the vein wall or through the sac (Fig. 2). Results of this type of operation have been reported by Matas,¹⁷ Elkin,¹⁸ Freeman,¹⁹ and others. We have been able to perform it successfully in four instances.

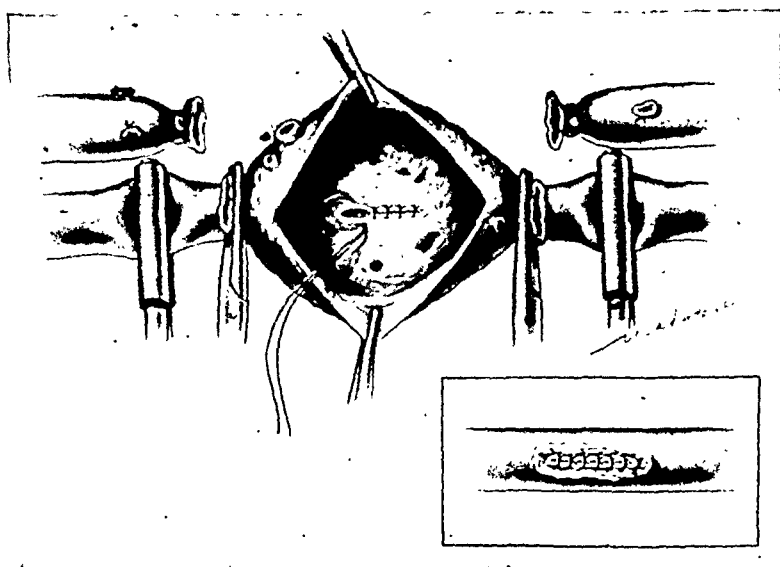


Fig. 2.—Repair of arteriovenous fistula through the sac. Vein has been ligated and divided. Insert shows excess sac excised.

III. *Ligation With Excision of All Involved Vessels.*—This operation usually gives the most satisfactory results. It takes advantage of the enormous collateral circulation which develops around an arteriovenous connection. I wish to point out that the term quadrilateral ligation is a misnomer. Rarely are there only four vessels involved. Collateral and new vessels form so rapidly and the vein and its branches dilate so quickly that innumerable vessels are encountered.

IV. *Obliteration Operation.*—In a few, obliteration similar to that used in arterial aneurysms is satisfactory.

ARTERIAL VARICES SYNDROME

We wish to draw attention to a group of patients often misdiagnosed and therefore inadequately treated. For a long time we have been aware that certain patients diagnosed as having varicose veins had pathology other than incompetent venous valves. Not infrequently adequate varicose vein surgery by competent surgeons has been followed by prompt recurrence. Careful observations have disclosed that such patients have innumerable small connections between the femoral artery and saphenous system (Fig. 3). This is not the simple aneurysmal varix in which one small artery branch dilates the saphenous vein, but is a congenital anastomosis by multiple small vessels which

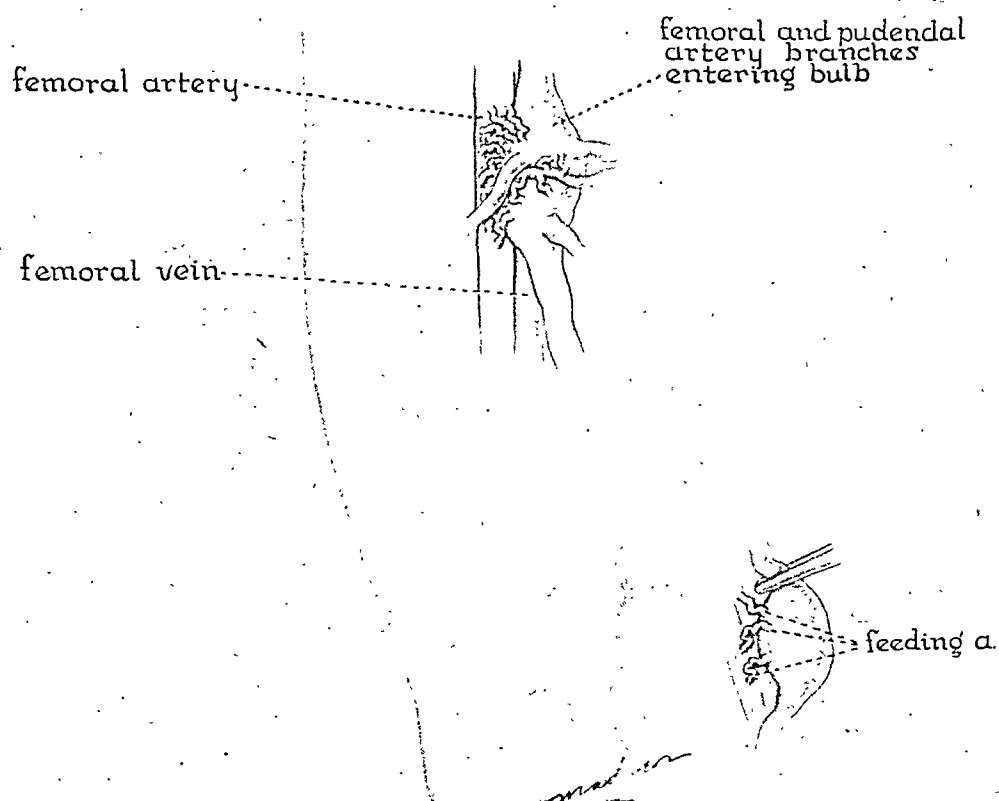


Fig. 3.—Drawing illustrating the anatomy of arterial varices.

suddenly open after having been obliterated for years. The diagnosis of this syndrome which we call arterial varices may be made by use of the following criteria:

1. The veins develop rapidly and extensively and remain partially filled on elevation of the limb. The vessels can be reduced on pressure, but fill more rapidly than ordinary dilatations on a basis of valve failure.
2. The veins occur more often on the lateral aspect of the leg or in the popliteal space (Figs. 4 and 5).



Fig. 4

Fig. 5

Fig. 4.—Typical appearance of arterial varices. These extreme dilatations appeared suddenly, unlike the slow development of varicose veins.

Fig. 5.—Anterior aspect of same patient as shown in Fig. 4.

3. They recur after the usual operation for varicose veins.
4. There is a greatly increased skin surface temperature which can be registered with the hand and always with the potentiometer.
5. There may be a bruit but usually this is not present. A bruit is caused by whirling blood. If the arteries are small and the vein large enough, the vein takes up the blood from the artery without the development of sufficient whirling to produce a bruit.
6. When the vein is opened, arterial blood is ejected synchronously with systole.
7. On pathologic section the vessel walls show more coats (Fig. 6) than a normal vein (Fig. 7) and less coats than an artery. This is the result of the reaction of the vessel to the circulatory trauma.



Fig. 6.—An arterial varix showing a vessel wall thicker than a vein. It does not have all the coats of an artery. Thickening is due to reaction of the vessel to arterial pressure ($\times 50$).

8. Oxygen saturation of the blood in these veins is higher than in ordinary veins.

It is suggested that in questionable cases the veins be incised and observed for arterial pulsations.²⁰

In the last 244 patients sent to us for varicose veins of a complicated nature, fifty-nine (almost 25 per cent) had varices which had recurred after operations performed by qualified surgeons. Of these fifty-nine patients, thirty-eight had arteriovenous connections. In the patients of this group in whom the varices were nonrecurrent, twenty-one had such connections. Thus, fifty-



Fig. 7.—Photomicrographic section of a normal vein ($\times 260$).

nine, or almost one in every four of those with advanced venous pathology, had undiagnosed arteriovenous connections rather than incompetent venous valves. It is difficult to obtain pathologic confirmation in all of these, since pathologists require certain walls to be present before they are willing to identify a vessel as an artery. In these fistulas, the vessel walls are usually im-

mature and poorly formed. Additional criteria for the pathologic recognition is being established.

Treatment of Arterial Varices.—The treatment requires:

1. Wide excision of the saphenous vein and its branches in the groin and popliteal space with resection of each arterial branch.
2. Excision of the saphenous vein at each incompetent point.
3. Extended and at times repeated excision of all dilated veins on the lateral aspect or popliteal area of the leg.
4. Inspection at six- to twelve-month intervals for recurrence points, and resection if they are large and injection if small.

SUMMARY

We wish to emphasize, the following:

1. The surgical treatment of arterial aneurysm must be individualized. Of the operations, the anastomosing or obliteration procedures potentially are the best. Obliteration of the aortic aneurysm is possible if certain technical difficulties are overcome.
2. Some arteriovenous aneurysms can be excised and anastomosed or the arterial defect sutured. In others quadrilateral ligation is not sufficient, but multiple resection of all the vessels involved in the process must be performed.
3. Congenital arteriovenous aneurysms may be quiescent for years, then become active and, like cancer, prove very difficult to eradicate. Neologically, arterionia is suggested.
4. A syndrome not emphasized before is presented. In this syndrome arteriovenous connections are misdiagnosed as varicose veins. This occurs in our practice in 25 per cent of those sent for advanced vein pathology. The syndrome of arterial varices can be diagnosed by attention to the features which have been pointed out. This syndrome should be suspected particularly if the veins are on the posterolateral or lateral aspect of the leg, if the patient is young, if there is increased local heat, and if the veins recur after adequate vein resection.

REFERENCES

1. Wright, I. S.: Vascular Diseases in Clinical Practice, Chicago, 1948, The Year Book Publishers, Inc.
2. Lake, M., Wright, I., and Pratt, G.: Arteriosclerosis and Varicose Veins. Occupational Activities and Other Factors, J. A. M. A. **119**:696, 1942.
3. Crile, G.: Quoted by Horsley, J. Shelton: Surgery of the Blood Vessels, St. Louis, 1915, The C. V. Mosby Company, p. 100.
4. Landon, L. H.: Cannula for Blood Vessels, J. A. M. A. **490**, 1913. Quoted by Horsley, J. Shelton: Surgery of the Blood Vessels, St. Louis, 1915, The C. V. Mosby Company, p. 112.
5. Blakemore, A. H., and Lord, J. W.: Blood Vessel Anastomosis by Means of a Non-suture Method Using Vitallium Tubes, New York, 1945; Thomas Nelson & Sons, Chapter XIII-A.
6. Blakemore, Arthur H., and Lord, Jere W.: A Nonsuture Method of Blood Vessel Anastomosis, Ann. Surg. **122**:476, 1945.

7. Pratt, G. H.: Surgical Treatment of Peripheral Aneurysm, Surg., Gynec. & Obst. 75:103, 1942.
8. Pratt, G. H.: Traumatic Aneurysms of the Extremities, Am. J. Surg. 71:743, 1946.
9. Biggers, I. A.: The Surgical Treatment of Aneurysm of the Abdominal Aorta, Ann. Surg. 112:879, 1940.
10. Matas, R.: Aneurysm of the Abdominal Aorta at Its Bifurcation Into the Common Iliac Arteries, Ann. Surg. 112:909, 1940.
11. Elkin, D. C.: Aneurysm of the Abdominal Aorta, Ann. Surg. 112:895, 1940.
12. Reid, M. R.: Quoted by Biggers.
13. Pearse, H. E.: Cellulose and Cellophane Products in Vascular Surgery. Presented at the Meeting of the Society for Vascular Surgery, Chicago, June 20, 1948.
14. Poppe, J. K., and de Olivera, H. R.: Treatment of Syphilitic Aneurysms by Cellophane Wrapping, J. Thoracic Surg. 15:186, 1946.
15. Blakemore, A.: Electrothermic Coagulation of Aneurysms, New York, 1945, Thos. Nelson & Sons, Chapter XII-B.
16. Moore and Corradi. Quoted by Babcock.²¹
17. Matas, R.: Endoaneurysmorrhaphy, Ann. Surg. 27:161, 1903.
18. Elkin, D. C.: Arteriovenous Aneurysm, Surg., Gynec. & Obst. 80:217, 1945.
19. Freeman, N. E.: Arterial Repair in the Treatment of Aneurysms and Arteriovenous Fistulae, Ann. Surg. 124:888, 1946.
20. Wright, I. S.: Personal communications.
21. Babcock, W. W.: Operative Decompression of Aortic Aneurysm by Carotid Jugular Anastomosis, Surg. Clin. North America 9:1031, 1929 (Phila. Number).
22. Blalock, Alfred: Discussion of Blakemore and Lord, Ann. Surg. 122:475, 1945.
23. Murray, Gordon, and Janes, J. N.: The Healing of Arteries and Their Relationship to Secondary Hemorrhage, Surgery 18:624, 1945.

PLASMA AND BLOOD INFUSION FOLLOWING MYOCARDIAL INFARCTION

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ACCOMPANYING or shortly succeeding myocardial infarction, a shock-like state with fall in both systolic and diastolic blood pressure has long been recognized as a frequent occurrence. Master and associates¹ studied 205 patients surviving attacks of acute myocardial infarction, 57 per cent of whom developed an abrupt fall of blood pressure within the first three days. This percentage included patients recovering from an immediate fall and exhibiting secondary depressions of their blood pressures. These authors conclude from the study of 538 patient-attacks that death generally occurred if the systolic blood pressure at any time fell below 80 millimeters of mercury. Likewise, if patients had been previously hypertensive, the fatality rate was materially elevated when the blood pressure fell below 100 mm. Hg, namely 50 per cent in that group, as contrasted to 29 per cent for the entire series. Mintz and Katz² reported a shocklike state in 6.9 per cent of 524 patients with acute myocardial infarction and a fatality rate of 77.8 per cent in the group with shock, as contrasted to 20 per cent in the entire series.

Even in such patients whose blood pressure returns spontaneously to more normal levels the occurrence of heart failure or death is frequent, indicating that extensive damage to the myocardium exists. However, certain patients recover and even maintain an adequately functioning myocardium. Recovery depends upon the availability of adequate circulation not only to the infarcted area but to the entire myocardium through all channels, including collateral arteries.

Recovery of an effective head of blood pressure in the aorta and the coronary arteries is essential, therefore, to prevent not only myocardial failure but also secondary myocardial infarction in areas supplied by narrowed arteries. Inadequate circulation elsewhere in the body, notably in the brain and the kidneys, is responsible for serious sequelae to myocardial infarction. Impairment of renal function has been generally found by the authors to follow myocardial infarction and in sustained hypotension has probably contributed to pulmonary edema and death in certain patients. Certain cases will be discussed later with illustrations. Reference is made to Case 1 (Fig. 2).

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Presented at the Twenty-first Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

The level of arterial pressure at which coronary blood flow becomes ineffective probably differs in each individual, as illustrated by the higher mortality in hypertensive patients, as contrasted to normotensive persons whose systolic blood pressure falls below 100 millimeters of mercury.¹ Thus, in a hypertensive woman (Case 5, Fig. 3), pallor, cyanosis, sweating, and faintness were present when her blood pressure fell from 186/120 to 96/68, whereas normotensive patients rarely exhibited such signs until the systolic blood pressure fell below 86 millimeters of mercury. Normally, hypotensive individuals may not show such evidence of circulatory insufficiency until their blood pressure reaches proportionately lower levels.

For these several reasons attempts have been made to correct the persistent severe hypotension of myocardial infarction by various means. Caffeine, Coramine, ephedrine, Paredrine, Neosynephrine, and epinephrine are among the drugs used, but the general clinical experience is that these substances are either ineffective or only transiently beneficial.

Transfusion has been performed by Gold,³ Schwartz,⁴ De La Chapelle,⁵ Segal,⁶ Levine,¹⁶ and others as a means of elevating and sustaining the blood pressure. The objective of transfusion is to correct the fall in blood pressure associated with the shocklike state of myocardial infarction but, in so doing, not further to handicap circulatory efficiency.

The cause of the shocklike state is not clearly established at present. Unknown hormonal and/or neurogenic factors may initiate this abnormal circulatory state. To what extent disturbed peripheral vascular functions contribute to it is not known.

There is a general belief, shared by Stead and Ebert,⁷ Fishberg,⁸ Murray,⁹ Prinzmetal,¹⁰ and Mendlowitz and his associates,¹¹ that there is diminished left ventricular output. This could be due to: (1) Diminished myocardial competence as evidenced by the occurrence at times of prolonged circulation time and elevated venous pressure. The inconstancy of these findings suggests either that their appearance is associated with definite degrees of incompetence or that there is a different causal mechanism which is not constantly operating in "infarction shock." (2) Depletion of effective circulating blood volume similar to that which occurs in hemorrhagic and traumatic shock. Hemoconcentration and hypovolemia generally occur in this state but do not occur concomitantly or in the same sequential degrees as the fall in arterial blood pressure. In two patients referred to by Stead and Ebert,⁷ "shock" was not increased by therapeutic bleeding; this further suggests that faulty venous return was not responsible for the shocklike state. (3) *Ballooning of muscle* or an "expansion chamber" effect has been observed by Murray⁹ and by earlier investigators to be inconstantly formed from the myocardium surrounding the infarct, as produced in dogs by ligation of the left anterior descending coronary artery. Such noncontractile zones, succeeding an attack of acute myocardial infarction and involving much larger areas of the heart muscle than the actual infarct, have been demonstrated in man by fluoroscopy and roentgenkymography by Dack and associates¹² and by others. Murray⁹ demonstrated

in dogs an improvement in aortic blood pressure and in cardiac output by resecting this area with the infarct.

Prinzmetal and his associates¹⁰ and Corday and co-workers¹³ reported the development of similar inactive areas in dogs on ligating the left descending coronary artery. Such areas are inconstant and recurrent in the absence of shock but constant following hypoxia or hemorrhagic shock. By transfusion after hemorrhagic shock, these workers restored the blood pressures to normal, and this was followed by resumption of contractions in these dilated areas surrounding the infarcts. After hypoxia, resumption of normal oxygenation of the blood produced a similar effect.

In clinical myocardial infarction, sustained shock and presumably dilatation of ventricular muscle commonly occurs without a complicating factor such as the bleeding used by Prinzmetal. However, the conditions are sufficiently similar to suggest that increasing the volume of blood entering the heart may have a beneficial result in human myocardial infarction. Thus, by obtaining better filling of the dilated chamber, a larger output would be expected according to Starling's law. None of these theories is uniformly supported by the available data, but at least certain hemodynamic conditions already referred to^{2,3} are known to be improved by transfusion.

Indications for Intravenous Infusions.—The development of pallid cyanosis, faintness, sweating, and abrupt fall in blood pressure or critical hypotension were the indications which led us to resort to infusion in the patients with myocardial infarction whose cases are being presented. Thus, the blood pressures at the time of the first infusion varied from 55/40 to 88/58.

In Case 6, one transfusion, and in Case 7, three additional transfusions were given on successive days after recovery from the initial shock in an attempt to sustain presumably effective blood pressure (88/64 to 100/76). A rise of systolic blood pressure of 16 mm. Hg or more was considered a successful result and this was invariably maintained for three and one-half hours or more.

Dangers of Intravenous Infusions.—The possible dangers of infusion would appear to be (1) the abrupt overloading of the left ventricle, especially in the presence of marked pulmonary edema, and (2) increasing right ventricular failure as evidenced by markedly elevated venous pressure. The rate and amount of infusion as well as the selection of patients for this procedure should be governed by an appreciation of these dangers.

It is likewise recognized that inadequate amounts of blood or plasma or too slow a transfusion rate would not materially modify hypovolemia or faulty circulatory dynamics. Too long a delay in instituting transfusion as well as slow rate of delivery of blood are well recognized causes for failure to reverse hemorrhagic shock^{14,15}. These may be causes of failure of transfusion to alter the shocklike state of myocardial infarction.

METHOD AND RESULTS

Eleven patients, seven men and four women, ranging in age from 44 to 65 years, were given thirty blood and whole plasma intravenous infusions by the gravity method (Table I). The location of the infarct, as diagnosed by the electrocardiogram and in five of the cases by electrocardiogram and autopsy findings, was in the anterior wall and septum of the left ventricle in four cases and in the posterior wall and septum of the left ventricle in seven. Five patients, including the four women, had essential arterial hypertension. Four had had previous myocardial infarctions, two anterior in both episodes, one anterior with a previous posterior, and one posterior with a previous anterior. Two patients had a history of angina pectoris and five had had no symptoms of coronary circulatory insufficiency. None of these factors apparently influenced the degree of success of infusion nor the duration of life after this procedure.

Twenty-two citrated whole blood and eight pooled human plasma* infusions were used. Two patients were given one transfusion, four were given two, two were given three, one was given four, and two were given five transfusions. Five hundred milliliters were given six times, 375 ml. once, 300 ml. once, 250 ml. twenty-one times, and 175 ml. once. Five were given at rates of 1.0 to 1.9 ml. per minute, fourteen were given at rates of 2.0 to 2.9 ml. per minute, three were given at 3.0 to 3.9 ml. per minute, seven were given at 4.0 to 5.0 ml. per minute, and one was given at a rate of 8.3 ml. per minute. No untoward febrile or other reactions occurred within six hours after the infusions.

Only one of the eleven patients recovered and was discharged from the hospital as asymptomatic. However, three patients had abrupt deaths after recovery from "shock": Case 4 after nine hours, Case 8 after eight days, and Case 11 after three days. Case 5, a formerly hypertensive woman with nephrosclerosis, died with progressive pulmonary edema. Her blood pressure ranged from 112/80 to 140/96 for six days prior to death.

Four patients had only a single episode of hypotension. Of these, three were unaffected by transfusion and death supervened. Three patients had two episodes. In at least one instance in each patient this was improved by infusion, and one patient spontaneously recovered from another. Three patients had three episodes, in all of which infusion was effective at least once, and in one of these three patients spontaneous recovery occurred twice. One patient had four episodes; the first three episodes responded transiently to infusion, the response lasting from three and one-half to nine hours. The fourth episode was not treated; hypotension persisted and resulted in death after twenty-four hours.

Of the twenty-three separate episodes of hypotension, five terminated in spontaneous recovery, eleven responded to infusions, and seven ended in death.

*Standard Army and Navy package. Normal human plasma, dried, with pyrogen-free distilled and sterilized water; representing 250 c.c. or 500 c.c. original normal plasma. One-tenth per cent .WV citric acid and 1:50,000 phenyl mercuric borate added.

TABLE I. EFFECT OF BLOOD AND PLASMA INFUSION IN ELEVEN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

CASE	LOCATION OF INFARCT	PREVIOUS INFARCT OR ANGINA PECTORIS	PRIOR BLOOD PRESSURE	BLOOD PRESSURE AT INFUSION*	BLOOD PRESSURE AFTER INFUSION	BLOOD PRESSURE SUSTAINED THREE HOURS†	DURATION HYPO-TENSION BEFORE INFUSION (HR.)	RATE OF INFUSION (ML. PER MIN.)	AMOUNT OF INFUSION (ML.)	INFUSIONS EFFECTIVE (16 MM. HG. +) —	SURVIVAL AFTER FIRST INFUSION				
											3-15 HR.	48-72 HR.	72 HR.-4 DAYS	8 DAYS	DIS-CHARGED ALIVE
1 (L. S., M., 55)	Ant.	Post.	120/82	70/53	90/70	+ 4 hr.	1	3.7	500P	3	X				
2 (H. C., M., 56)	Post.	0	165/100	72/40	72/50	—	11	4.2	250B	2	X				
3 (L. C., M., 60)	Post.	Ant.	110/80	(80/64)-70/?	94/70	+ 9 hr.	2½, 18, 20	2.1, 3.3, and 4.2	250B, 250B, 250B	1 4 (No. 3)	X				
4 (D. S., M., 62)	Post.-Lat.	0	112/70	(88/58)-60/42	90/60	+ 3 hr. 40 min.	¼	3.1	250B	2	X				
5 (H. B., F., 65)	Post.	0	200/124	84/64	110/64	+ 3 hr. 30 min.	1½	2.0	175B	1 2 (No. 1)			X		
6 (R. R., F., 61)	Post.	0	170/100	74/60	98/78	+ 36 hr.	2½	2.8	250P	1 1 (No. 1)			X		X
7 (H. W., M., 44)	Post.	0	110/72	(84/40)-74/50	92/66	+ 5 wk. +	1½	2.4	250B	1 4 (No. 2)					
8 (L. R., F., 62)	Ant.-Sept.	Ant.	164/104	55/40	108/70 (Caffeine S.B. IV)	+ 23 hr.	½	4.1	250P	1 1				X	
9 (W. W., M., 49)	Ant.-Lat.	Ant. (2)	124/86	82/60	86/60	—	58	2.4	250B	4			X		
10 (M. L., M., 44)	Post.-Lat.	Ang. pect.	140/90	86/68	102/80-60/?	0	4	5.0	250P	1	X				
11 (M. B., F., 62)	Ant.	Ang. pect.	164/112	74/60	86/60-94/70 (½ hour)	+ 3 days	½	4.2	500B	1		X			

*The blood pressure is given in millimeters of mercury. Figures in parentheses are the initial pressures recorded at onset of the hypotension.

†The plus (+) sign indicates at least one "effective" infusion. The minus (—) sign indicates no "effective" infusion. The zero (0) sign in Case 10 indicates a transient effect, which was followed shortly by death.

In all cases except Case 3, where the data on three infusions are given, the data in Columns 6 through 10 represent the results of the first "effective" infusions, or, if ineffective, the first infusions given.

Bilateral pulmonary râles were present in eight of the eleven patients at the time of one or more of the infusions. They were limited to the lower lung bases in all patients but one (Case 10), in whom they were hilar and basal and coarser than subcrepitant in quality.

In seven instances no change occurred in the intensity of the pulmonary edema within three hours after infusion; in three the râles diminished; and in two (Cases 1 and 6) on the second infusion, with the blood pressure sustained at 94/78, they increased slightly. In Case 10, to be reviewed later, there was no increase in the moderately severe pulmonary edema, but the patient lapsed into coma at the completion of transfusion. The blood pressure fell after a transient rise and he died three hours later. This patient had an initial venous pressure of 24 cm. of isotonic sodium chloride solution.

In eight of the eleven patients at least one infusion produced a successful result. Where successful elevation of blood pressure was obtained in the seven patients receiving more than one infusion, this occurred in the first infusion in five cases, and in the second and in the third infusions in one case each where prior infusions had failed.

The percentages of success with 500 and 250 ml. of blood or plasma seemed to be the same. In Case 8 a rise of blood pressure of 10 mm. Hg occurred after 100 ml. of blood had been given; in Case 5 a rise of 26 mm. Hg with a total of 175 ml. of blood; and in Case 10, with a high initial venous pressure of 24 cm. of normal salt solution, a rise of 26 mm. Hg took place with 100 ml. of blood given in twenty-five minutes.

Table II presents the infusions resulting in significant rises and maintenance of blood pressure. There were three instances of systolic pressure elevations of 16 to 18 mm. Hg, seven of from 20 to 30 mm. Hg, and one of 53 millimeters of mercury. In two instances transfusion produced no significant rise of diastolic pressure, in five transfusion produced a rise of from 10 to 15 mm. Hg, in three a rise of from 15 to 20 mm. Hg, and in one a rise of 30 millimeters of mercury.

TABLE II. DEGREE OF DURATION OF SIGNIFICANT ELEVATION OF BRACHIAL ARTERIAL BLOOD PRESSURE FOLLOWING ELEVEN BLOOD OR PLASMA INFUSIONS

Systolic blood pressure elevation (mm. Hg)	16	18	20	24	26	30	53	
Number of instances	1	2	4	1	1	1	1	
Diastolic blood pressure elevation (mm.Hg)	0	2	10	14	16	18	20	30
Number of instances	1	1	3	2	1	1	1	1
Duration of sustained elevation of systolic blood pressure	3½° to 4°	6°	7°	9°	22°	39°	72°	5 wk. +
Number of instances	3	1	1	2	1	1	1	1

The maintenance of the elevated blood pressure was observed from three and one-half to four hours in three instances, from six to nine hours in four instances, from one to three days in three instances, and to the time of discharge after five weeks in one patient.

The packed cell volume seemed to vary in the individual patients with the degree of "shock" exhibited and invariably increased with advancing heart failure and pulmonary edema. Six of ten patients exhibited a packed cell volume of over 47 c.c. per cent within twenty-four hours of hospital admission. Thus, Case 3 with relatively little shock at entry had a packed cell volume of 39 c.c. per cent, whereas Case 2 with severe hypotension initially had 51 c.c. per cent, which rose to 55 per cent before death.

Total serum protein varied from 5.5 to 6.8 Gm. per cent in the five cases in which determinations were made. Only minor changes were noted in the packed cell volume and total protein following infusion in six cases so studied. For example, Case 1 had a packed cell volume of 56 c.c. per cent one hour before a 500 ml. plasma infusion and a total protein of 6.8 Gm. per cent. Two hours after transfusion there was a packed cell volume of 60 c.c. per cent and a total protein of 6.7 Gm. per cent. Fourteen hours later, one and one-half hours after a 250 ml. transfusion of blood, the determinations were 50 and 5.8, respectively, and twenty-four hours later, after another 250 ml. blood transfusion, the packed cell volume was 54 c.c. per cent and the total serum protein was 6.5 Gm. per cent.

Changes such as were observed cannot at present be assigned solely to the infusions because fluctuations in the degrees of heart failure and altered peripheral vascular dynamics probably occurred and influenced the packed cell volume and protein concentrations.

In four patients in the recumbent position determinations of venous pressure by direct measurement were made in the antecubital vein, immediately prior to and following five infusions. The results show that little elevation follows when venous pressure is not over 13 cm. of normal salt solution. Case 1, receiving 250 ml. of blood at a rate of 2.5 ml. per minute, demonstrated a rise from 13 to 17 centimeters. Case 9 showed on the second transfusion a rise from 8 to 11 cm. with 250 ml. of blood at 1.7 ml. per minute and on the third transfusion, no significant change, namely 10.5 to 11 cm. after 250 ml. of blood at 1.4 ml. per minute. The rate of transfusion in this patient was probably too low since the arterial blood pressure actually fell during both transfusions. The circulation time, arm-to-tongue, was unchanged at thirty-five seconds on the second transfusion and was thirty-seven seconds prior to and forty seconds following the third transfusion, confirming the unaltered state of vascular congestion.

Case 11 illustrated that a 500 ml. blood transfusion at 4.2 ml. per minute had no effect on the venous pressure, which was 9.2 cm. prior to and 9 cm. following the treatment. The arterial blood pressure rose from 72/60 to 94/70 in the same period of time.

Case 10 (Fig. 6) was an example of the probably harmful influence of infusion in a patient with a high venous pressure and marked pulmonary edema.

An infusion was given because his blood pressure, which had been 110/70 on the fifth day after the onset of the myocardial infarction, fell to 84/72 on the sixth day. The low blood pressure was accompanied by chest pain, pulmonary edema, and cyanosis, and failed to rise after the intravenous administration of 1.0 Gm. of caffeine and sodium benzoate.

The circulation time in Case 10 was seventeen seconds and the venous pressure, 24 cm. of normal salt solution at the start of the infusion of 250 ml. of plasma at 5.0 ml. per minute. After 100 ml. had been given the venous pressure was 26.5 cm. and the blood pressure was 102/80. After completion of the infusion in fifty minutes, the venous pressure was 37 cm., and the blood pressure was 88/70, and although the cyanosis was somewhat lessened and the pulmonary râles had not increased, the patient lapsed into coma. The heart sounds, which had become louder during the infusion, became inaudible ten minutes later and the blood pressure fell to 62/50. The patient died two hours later without regaining consciousness.

From this case history it may be assumed that a high venous pressure is evidence of adequate venous return and that only harm can result from further addition to the blood volume. Although death may have been coincidental, in as much as circulatory failure was advancing rapidly at the time of the infusion, it is likely that the cardiac failure was hastened by that procedure.

Comment.—Three factors seem to be important in gaining an effective elevation of blood pressure by infusion, namely (1) early institution of the procedure after the onset of hypotension, (2) a sufficiently rapid rate of transfusion, and (3) the degree of hypotension. The influence of the first two of these factors may be illustrated by Fig. 1, in which the thirty infusions are graphically shown in relation to the rate of infusion and the time elapsed after onset of each episode of hypotension for which the treatment was given. In ten of the eleven patients in whom successful results were obtained the transfusions were given within four hours of the onset of marked hypotension; in only four of the nineteen patients in whom the procedure was unsuccessful were the infusions given within this period. The successful transfusion in Case 3, recorded as having been given twenty hours after onset of hypotension, actually followed by two hours a similar transfusion of 250 ml. of blood and produced a sustained elevation of blood pressure for nine hours.

In the three failures where treatment was given four hours or less after onset of "shock" the infusions were given at rates of 4.6, 2.1, 1.7, and 1.4 ml. per minute, respectively. All of the successful infusions were given at rates over 2.0 ml. per minute and seven of the eleven were given at rates of from 2.5 to 4.3 ml. per minute. In Case 8, a woman with long-standing hypertension, the second transfusion was given when the blood pressure was fluctuating between 92/58 and 110/76, and was resorted to not only in an attempt to stabilize the pressure but also because of dehydration and inanition accompanying anorexia and nausea. No immediate ill effect followed this infusion, which was administered at a rate of 8.3 ml. per minute, although pulmonary edema developed ten hours later following a hypodermoclysis of 1,000 ml. of normal salt solution.

30 Infusions in 11 Cases of Myocardial Infarction.

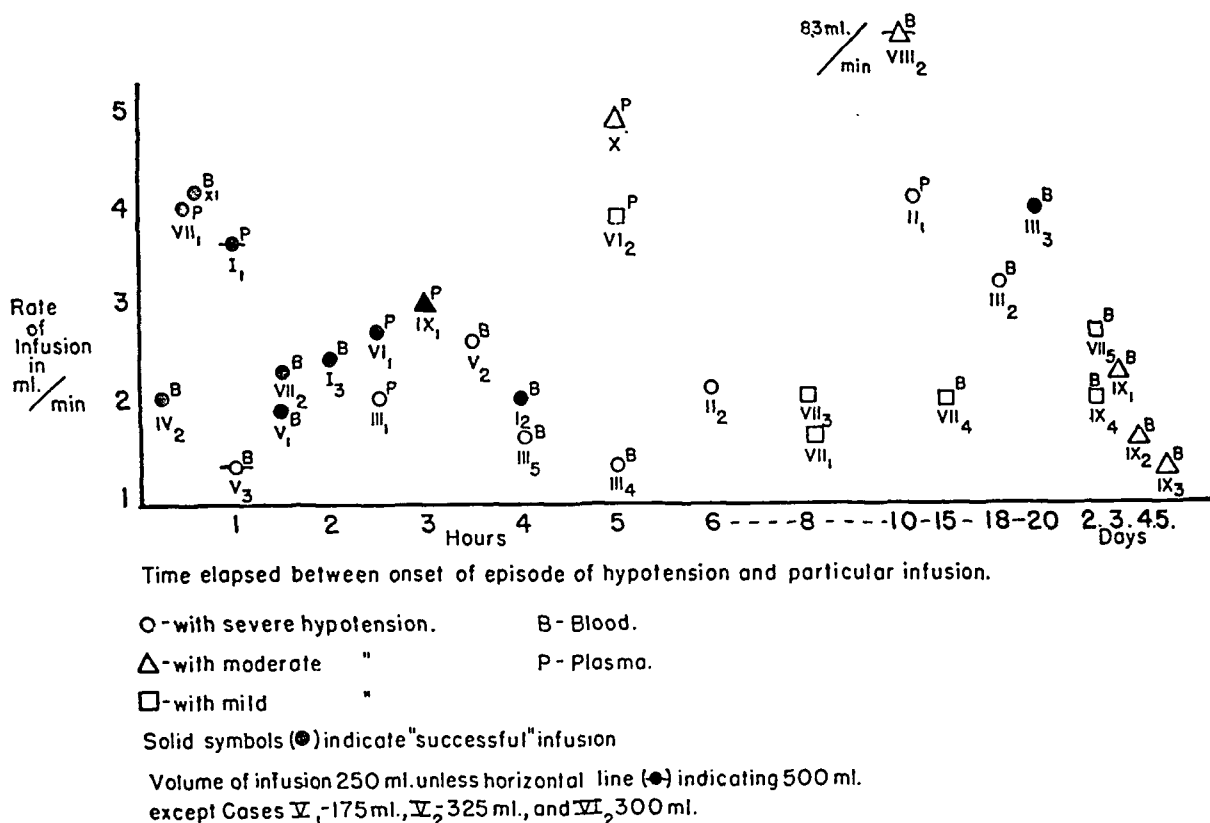


Fig. 1.—Relation of success of intravenous infusion to rate of flow and to duration of hypotension prior to start of infusion. Roman numerals indicate case number; Arabic numerals, the number of infusions in each particular case.

The patients who responded best to infusion were, in general, those with the most severe hypotension. Thus, of the eleven patients in whom infusions gave "successful" results, nine had initial systolic blood pressures of 80 mm. Hg or less, and the remaining two had pressures of 84 and 88 mm. Hg, respectively. The former was a woman with previous severe hypertension (Case 5). Of the nineteen patients who were classified as failures, seven had initial systolic blood pressures of 82 mm. Hg or lower, four had pressures of from 86 to 88 mm. Hg, and eight had pressures over 90 millimeters of mercury. In Case 7 (Fig. 4), three of the four infusions were given largely to sustain blood pressure, and in Case 9 the symptoms of shock were more evident than the preinfusion blood pressures (88/60, 100/70, 92/70, and 82/76 mm. Hg) indicated.

Certain of the case findings are illustrated in Figs. 2 to 6 (Case 1 in Fig. 2, Case 5 in Fig. 3, Case 7 in Fig. 4, Case 8 in Fig. 5, and Case 10 in Fig. 6).

Case 1 illustrates three successful responses to infusion, but the failure to sustain the blood pressure more than seven hours at any time led to cessation of treatment. Perhaps continued infusions might have resulted in recovery.

Case 5 demonstrates two ineffective transfusions following ten hours after a small but apparently successful one. This patient recovered from "shock" but later died from progressive pulmonary edema. In spite of low plasma

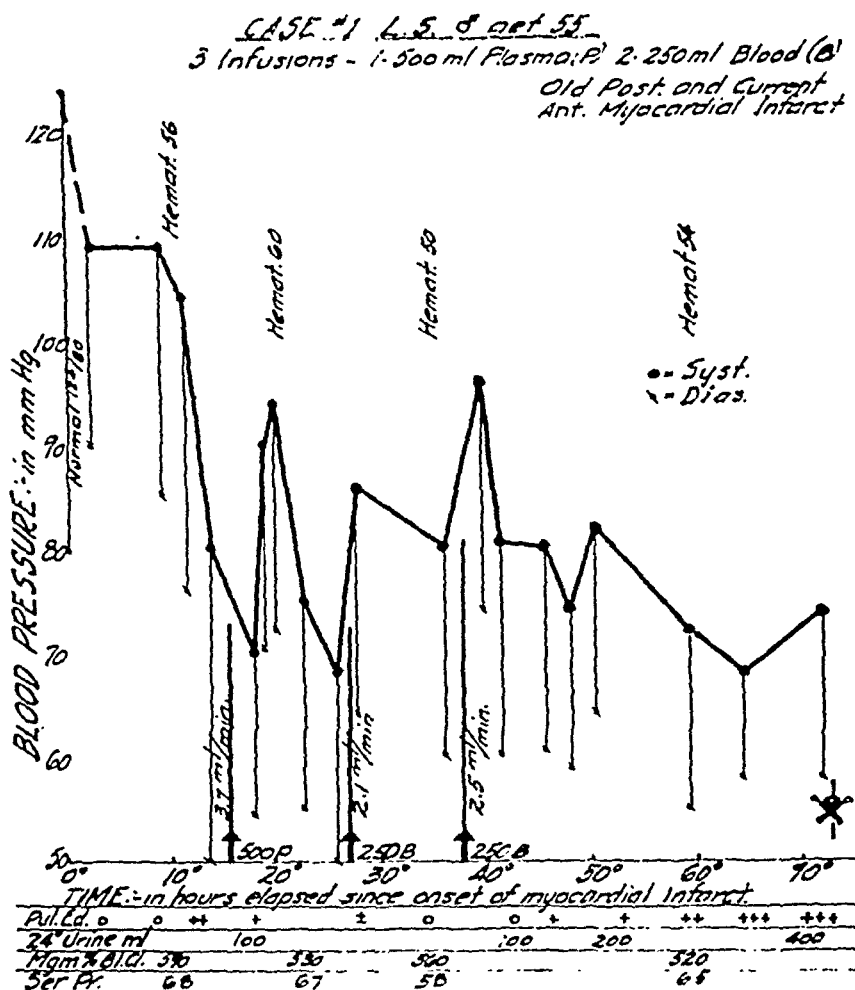


Fig. 2.—Response of blood pressure to infusions in Case 1. Additional data on occurrence of pulmonary edema, total urine output in indicated periods, and plasma chlorides and serum protein at various times after the onset of myocardial infarction.

chlorides, the retention of sodium, which was augmented by hypodermoclyses of normal salt solution and glucose, was probably partially responsible for this fatality.

Case 7 illustrates a spontaneous recovery from shock, a second episode with successful response to transfusion, and then the maintenance of moderate but constant hypotension following three additional transfusions. This man recovered to leave the hospital asymptomatic.

Case 8 illustrates a striking effect of early transfusion. This may have been aided by intravenous caffeine and sodium benzoate given in a dose of 1.0 Gm. one-half hour before the infusion of 250 ml. of blood, but it was unlikely that caffeine produced the sustained effect exhibited. This patient would probably have survived, as the evidences of shock were absent for six days, if a secondary myocardial infarction had not supervened.

Case 10 illustrates the harmful effect of infusion when a high venous pressure exists.

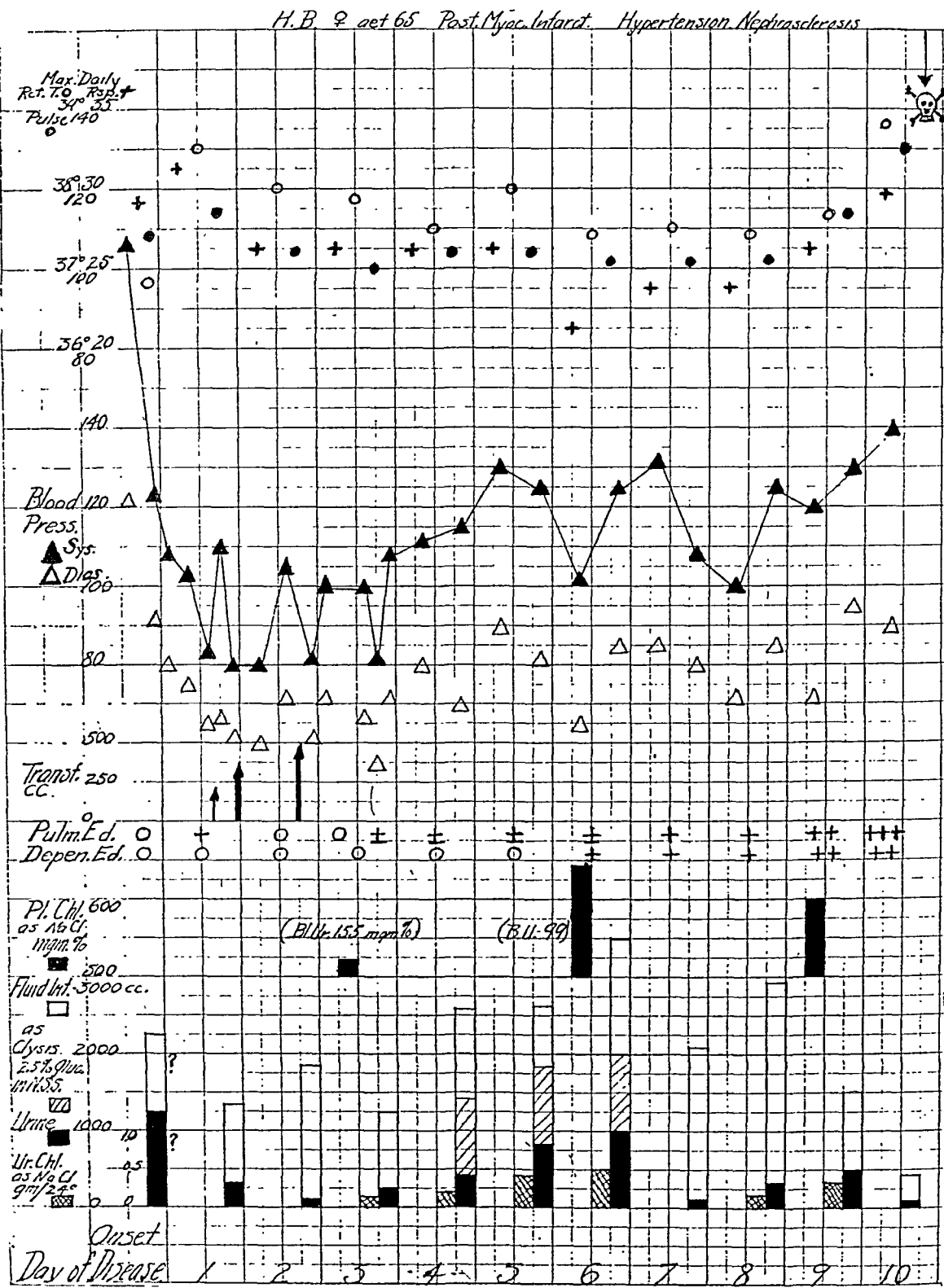


Fig. 3.—Response of blood pressure to infusions in Case 5. Clinical data as in Fig. 1 with daily fluid intake and urine output and urine chlorides, plasma chlorides, and blood urea at various times after the onset of myocardial infarction.

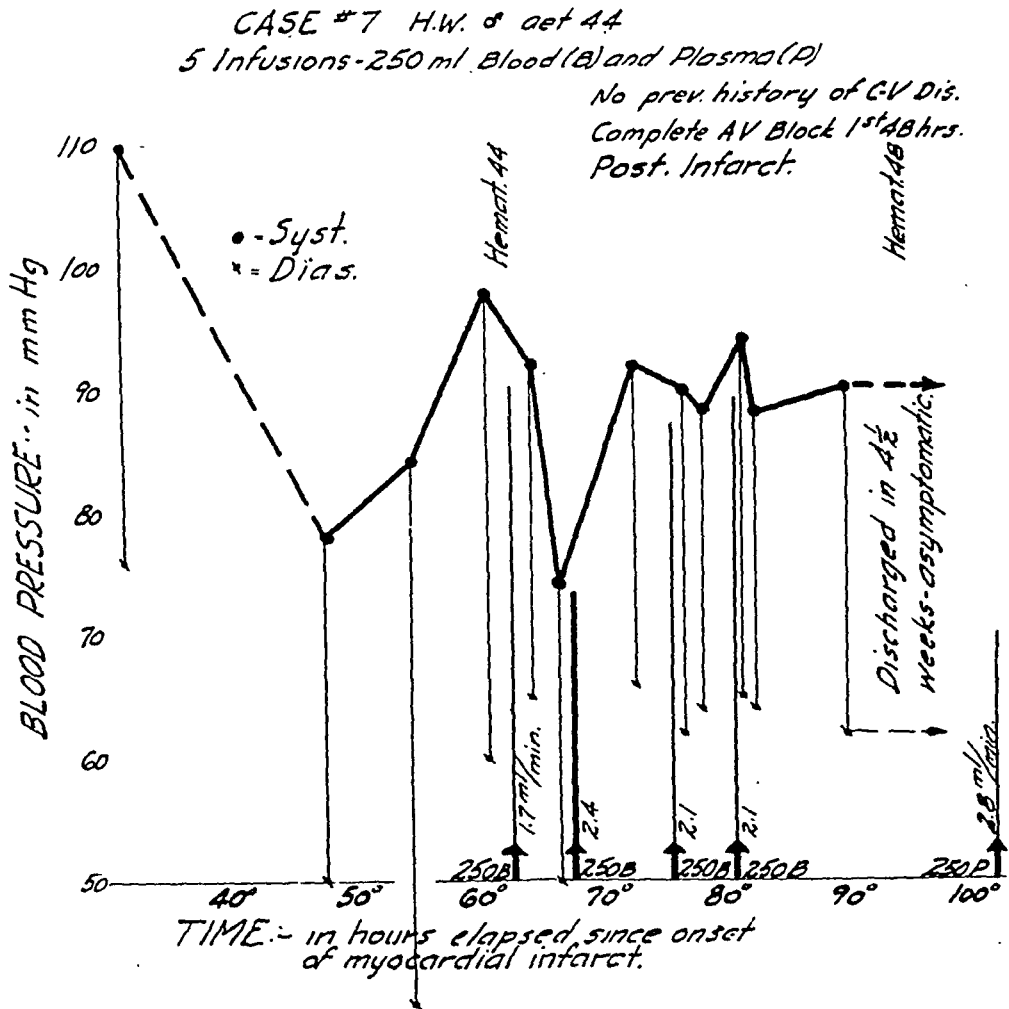


Fig. 4.—Response of blood pressure to infusions in Case 7. Note that the first infusion was ineffective, the second was effective, and the third and fourth infusions were given in an attempt to maintain elevated blood pressure.

Case 11 is an example of another effective elevation of blood pressure following blood infusion, which was sustained for a sufficiently long period to conclude that this patient would probably have survived the initial attack of myocardial infarction if a secondary attack had not occurred (not illustrated).

DISCUSSION

It is recognized that the reasons are not well established for the success or failure of blood or plasma infusions to elevate effectively or to sustain blood pressure through a critical period following myocardial infarction with eventual survival of the patient. Perhaps the regime employed in Case 7, repeating infusions after an initial satisfactory response, without recurrent severe shock may result in more survivals. The indications for such repeated transfusions as well as for the mode of administration of the individual infusion will probably depend on the development and application of techniques for more exact study of the blood volume, cardiac output, and pulmonary and peripheral circulation than have been applied to this series of patients.

SUMMARY AND CONCLUSIONS

Thirty intravenous infusions of blood and normal human plasma were given to eleven patients exhibiting one or more shocklike episodes following acute myocardial infarction.

Whereas only one of the eleven patients recovered and was discharged asymptomatic, the results of the infusions seemed to have carried four of them over critical periods of hypotension, and death resulted later from secondary infarction or heart failure.

No apparent harmful effects of infusion of blood or plasma were demonstrated except in a single patient with a high initial venous pressure. The infusions seemed to be more effective when the systolic blood pressure was under 85 millimeters of mercury. They were likewise more effective when given prior to four hours after marked hypotension developed and at rates of at least 2.0 and preferably of from 2.5 to 5.0 ml. (or 8.0 ml.) per minute.

It is assumed that the use of blood or plasma infusions probably cannot alter the immediate destruction of the myocardium by ischemia and that death will follow such destruction when it is extensive. However, the favorable effects may be due to (a) reduction of the effects secondary to shock (improved irrigation of the coronary bed); (b) maintenance of normal or excess venous return to the heart to preserve cardiac output in the presence of the dilated left ventricle; (c) reduction of the area of dilatation of the myocardium surrounding the infarcted zone, a process which may possibly cause or increase the shocklike symptoms and hypotension.

One cannot predicate that all of the successful results were due to the infusions since spontaneous recovery of hypotension after myocardial infarction is common. However, the prompt response in most instances seems conclusive of a genuine therapeutic effect.

ADDENDUM

Six additional cases of infusion treatment of myocardial infarction shock have been observed since presentation of this paper. Four improved, three of whom were discharged as recovered.

REFERENCES

1. Master, A. M., Jaffe, H. L., Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During, and After Coronary Occlusion, *AM. HEART J.* 26:1, 1943.
2. Mintz, S. S., and Katz, L. N.: Recent Myocardial Infarction, *Arch. Int. Med.* 80:205 1947.
3. Gold, H.: Cornell Conference on Therapy, *Am. J. Med.* 1:296, 1946.
4. Schwartz, W. B.: The Treatment of Shock Accompanying Myocardial Infarction, *AM. HEART J.* 33:169, 1947.
5. De la Chapelle, C. E.: The Management of the Acute Episode in Coronary Occlusion, *Bull. New York Acad. Med.* 19:201, 1943.
6. Segal, H. A.: Personal communications.
7. Stead, C. A., Jr., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart, *Arch. Int. Med.* 69:369, 1942.
8. Fishberg, A. M.: Heart Failure, ed. 2, Philadelphia, 1940, Lea & Febiger, p. 460.
9. Murray, G.: The Pathophysiology of the Cause of Death From Coronary Thrombosis, *Ann. Surg.* 126:523, 1947.

10. Prinzmetal, M.: Coronary Artery Occlusion in Man and Animals, Studied by Radioactive Isotopes. Address given at 29th Annual Session, American College of Physicians, San Francisco, April, 1948.
11. Mendlowitz, M., Schauer, G., and Gross, L.: Hemodynamic Studies in Experimental Coronary Occlusion, *AM. HEART J.* 13:664, 1937.
12. Dack, S., Sussman, M. L., and Master, A. M.: Roentgenkymogram in Myocardial Infarction. Part I. Abnormalities in Left Ventricular Contraction, *AM. HEART J.* 19:453, 1940.
13. Corday, E., Spritzler, R., Krueger, H. E., Bergman, H. C., and Prinzmetal, M.: Experimentally Produced Coronary Artery Insufficiency. Address given at Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, 1948.
14. Wiggers, C. J.: The Failure of Transfusions in Irreversible Hemorrhagic Shock, *Am. J. Physiol.* 144:91, 1945.
15. Cole, J. T.: Method of Treating Massive Obstetric Hemorrhage, *J. A. M. A.* 135:142, 1947.
16. Levine, S. A.: *Clinical Heart Disease*, ed. 3, Philadelphia, 1945, W. B. Saunders Company.

THE SOUNDS AND MURMURS IN COARCTATION OF THE AORTA

A STUDY BY AUSCULTATION AND PHONOCARDIOGRAPHY

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INTRODUCTION

CONSIDERABLE interest in the diagnosis of coarctation of the aorta has recently been stimulated by the successful surgical treatment of this condition. Although the murmurs which have been found in cases of coarctation of the aorta have been thought to be unimportant, the first suspicion of a congenital defect of the cardiovascular system is frequently aroused by the discovery of an abnormality on auscultation, and it is probable that further knowledge of the characteristic murmurs found in patients with this particular congenital defect will increase the frequency and accuracy of its diagnosis. With this objective in mind we have made, by auscultation and by phonocardiography, the following study of patients with coarctation of the aorta.

AUSCULTATORY SIGNS

Abbott,¹ in a comprehensive review of the literature up to 1928 on the subject of coarctation of the aorta, states that "a systolic murmur with maximal intensity along the left sternal border and heard also in the back, which is thought to be generated at the constriction, has been described (Laubry) as characteristic." She believes that other auscultatory abnormalities are caused by associated valvular lesions or are produced in the dilated and tortuous collateral channels.

A recent review of the subject by Reifenstein, Levine, and Gross² describes a systolic murmur over the precordium, especially at the base, and often in the back between the scapulae and alongside the lower dorsal spine. However, they consider that a systolic murmur in the back accompanying a murmur of only moderate intensity anteriorly is more diagnostic of coarctation of the aorta. Especially is this so in the rare instances when the murmur is louder behind than in front. They state that a diastolic murmur is not found in uncomplicated coarctation of the aorta and that when present it is associated with aortic valvular deformity or patency of the ductus arteriosus.

Taussig³ maintains that there is no cardiac mechanism in this condition to cause precordial murmurs or thrills, which are, according to her, the exception

rather than the rule. She states, however, that the occurrence of murmurs in unusual places, as over any of the vessels of the collateral circulation, is characteristic of coarctation of the aorta, and that not infrequently the occurrence of a murmur in the interscapular region first suggests the possibility of this defect.

Our observations on a small series of patients indicate that there are certain auscultatory features which have not been adequately described. We have studied the patients by phonocardiography in order to illustrate these features and also to demonstrate that there are characteristics of the sound vibrations occurring in coarctation of the aorta which are not recognized by auscultation.

AUSCULTATORY FINDINGS

The material from which this study has been made consists of auscultatory and phonocardiographic findings on fifteen patients with coarctation of the aorta in whom surgical cure had not been undertaken (Table I). The coarctation was considered to be uncomplicated in these patients, except for one in whom the additional diagnosis of aortic regurgitation was made clinically.

A systolic murmur over the precordium was heard in all the patients except one (in this patient no murmur was heard over the anterior chest). The murmur ranged in intensity from slight (Grade 2) to very loud (Grade 5). Its maximal intensity was at the base of the heart in eleven patients and at the apex of the heart in one patient, while it was of equal intensity at apex and base in two patients.

A systolic murmur over the back was heard in every instance. This murmur was maximal either at the midline or a few centimeters to one or the other side of the midline at some level between the second and fifth spinous processes. It was of greater intensity over the back than over the precordium in five patients (one of these being the patient in whom no murmur at all was heard in front).

A diastolic murmur over the base of the heart was heard in five of the fifteen patients. *A diastolic murmur over the dorsal spine* was heard in four of these five, and in two of them the murmur was of greater intensity over the back than over the precordium. In two additional patients a diastolic murmur was heard over the back while none was audible in front.

We have described earlier the opinions of authorities who believe that precordial murmurs are the exception rather than the rule, and that diastolic murmurs are never present in uncomplicated coarctation of the aorta. However, the murmurs of complicating deformities such as aortic stenosis and insufficiency and patent ductus arteriosus are not well conducted to the back, and we have not found significant murmurs over the collateral channels in the patients under our consideration. Therefore, we consider that systolic and diastolic murmurs over the dorsal spine, where they are not infrequently of

TABLE I. FINDINGS IN FIFTEEN PATIENTS WITH COARCTATION OF THE AORTA

PATIENT	SEX	AGE	AUSCULTATORY FINDINGS					PHONOCARDIOGRAPHIC FINDINGS			
			PRECORDIUM		BACK			PRECORDIUM		BACK	
			INTERCOSTAL SPACE AT WHICH MURMUR HAD MAXIMAL INTENSITY	SYSTOLIC MURMUR	DIASTOLIC MURMUR	SPINOUS PROCESS AT WHICH MURMUR HAD MAXIMAL INTENSITY	SYSTOLIC MURMUR	DIASTOLIC MURMUR	SYSTOLIC VIBRA- TIONS	DIASTOLIC VIBRA- TIONS	SYSTOLIC VIBRA- TIONS
L. M.	M	7	Second left	Grade 3	None	D 2	Grade 1	None	Present	Absent	Present
J. T.	M	9	Second left	Grade 3	None	D 4	Grade 3-4	None	Present	Present	Present
T. S.	M	11	Third left	Grade 3	Present	D 3	Grade 2	Present	Present	Present	Present
N. G.	M	19		None	None	D 2	Grade 2	None	Present	Absent	Present
J. B.	M	22	Second left, apex	Grade 2	Grade 2	D 5	Grade 3	Grade 1	Present	Present	Present
A. L.	M	22	Second right	Grade 3	None	D 3	Grade 2	None	Present	Present	Present
A. C.	M	27	First left	Grade 2	None	D 2	Grade 2	Present	Present	Present	Present
E. S.	M	28	Second right	Grade 2	None	D 2	Grade 2	None	Present	Absent	Present
L. M.	M	32	Second left	Grade 2-3	Grade 2	D 2	Grade 4	None	Present	Present	Present
I. M.	M	38	Second left	Grade 2-3	None	D 2	Grade 2	None	Present	Present	Present
E. C.	M	41	Apex	Grade 5	Grade 3	D 3	Grade 2	Grade 1-2	Present	Present	Present
J. D.	F	23	Apex, second left	Grade 2	Grade 1	D 3	Grade 2-3	Grade 1-2	Present	Present	Present
H. O.	F	27	Second left	Grade 3	None	D 5	Grade 2	None	Present	Present	Present
D. R.	F	33	Second left	Grade 2-3	None	D 4	Grade 1-2	None	Present	Present	Present
V. K.	F	47	Second left	Grade 3	None	D 2	Grade 2	Present	Present	Absent	Present

greater intensity than over the precordium, constitute a physical sign of uncomplicated coarctation of the aorta, and that these characteristic murmurs are usually accompanied by systolic, and occasionally also by diastolic murmurs heard anteriorly over the base of the heart.

PHONOCARDIOGRAPHIC OBSERVATIONS

In order to obtain a more accurate analysis of the sounds and murmurs in coarctation of the aorta and to demonstrate graphically inaudible vibrations, our fifteen patients were studied by phonocardiogram. The apparatus used was a Sanborn Tribeam phonocardiograph, with logarithmic and stethoscopic microphones and interchangeable chestpieces.^{4,5} The reasons for our choice of this instrument, together with a description of a satisfactory phonocardiographic technique, have been recently presented in a study of basal diastolic murmurs.⁶ In the present study we placed the microphone over that part of the patient's back at which the murmur was maximal. (These tracings were most satisfactorily obtained when the patient was lying prone with a pillow under his chest to allow forward movement of the shoulders, so that the scapulae might be more widely separated.) Further tracings were taken with the patient supine and the microphone placed over that part of the base of the heart at which the precordial murmur was maximal. The method of standardization of sound intensity described by Rappaport and Sprague⁷ was used in this study.

In the tracings taken from the back, a systolic murmur was recorded in every patient, which was to be expected, because this murmur was in every instance audible. Significant diastolic vibrations* were, however, recorded at the same location, not only in the six patients in whom a diastolic murmur was heard on auscultation, but in every one of the remaining nine patients.

Systolic vibrations were recorded from the base of the heart in all fifteen patients, although in one of these patients no systolic murmur was audible. Significant diastolic vibrations* were recorded from this area not only in the five patients in whom a diastolic murmur was audible but also in five additional patients.

These observations indicate a more frequent occurrence of systolic and diastolic vibrations than is found on auscultation. One reason a diastolic murmur may not be audible, although significant diastolic vibrations are recorded phonocardiographically, is that a loud systolic murmur or second heart sound may produce a fatiguing effect on the human hearing mechanism which persists into early diastole. Another reason is that, since the second heart sound is frequently inaudible over the back, the exact onset of diastole cannot be estimated and a murmur may be interpreted as systolic when it actually persists into early diastole.

As our phonocardiograms reveal, the first and second heart sounds may be recorded from the back, and when this is so they do not show appreciable transmissional delay. We have found, too, that when murmurs are widely con-

*Diastolic vibrations are considered significant if they show a period of maximal or minimal intensity which recurs in a similar location in subsequent cardiac cycles.

ducted over the precordium or into the back, their configuration on phonocardiography is not significantly altered. We have, therefore, in our patients with coarctation of the aorta, contrasted the configuration of the murmurs recorded from the back with that of the murmurs recorded from the precordium.

The murmur present over the dorsal spine in these cases was crescendo-decrescendo in character, starting a short interval after the onset of systole and often continuing into early diastole. In only two of these patients was the systolic murmur over the precordium similar in configuration to that over the dorsal spine. In both of these the murmur was of greater intensity over the back and was probably conducted to the precordium. In five additional patients the systolic murmur recorded from the back was of greater intensity than that obtained from the precordium. In these patients, however, the configuration of the murmur in the precordium was different, indicating that it contained vibrations which were not conducted from the back. Finally, in eight patients the murmur was louder in front and did not resemble the recording from the dorsal spine.

The diastolic vibrations recorded over the dorsal spine were decrescendo in configuration in twelve of the fifteen patients. In these twelve patients the envelope of the combined systolic and diastolic vibrations was fusiform in shape. In the three remaining patients inaudible diastolic vibrations were recorded which were minimal in intensity in early diastole and gradually increased in intensity in later diastole. In only one patient the precordial diastolic vibrations were of the same configuration as those from the back but of lower intensity. In two other patients the diastolic vibrations, while similar in configuration, were of greater intensity over the precordium.

In seven patients diastolic vibrations from the precordium had a crescendo-decrescendo configuration, with maximal intensity shortly after the second heart sound. In six of these, the vibrations also differed from those recorded from the back in that they were of greater intensity than the vibrations in the latter part of systole. The diastolic vibrations in these seven patients resembled in configuration those of the basal diastolic murmur of aortic or pulmonary insufficiency as described by Wells, Rappaport, and Sprague.⁶ This would, of course, suggest the additional diagnosis in these cases of a congenital bicuspid aortic valve. Only one of the seven patients has died, but autopsy confirmed this diagnosis in his case, a full description of which has been presented by Clark and Ferminger.⁸ In another of the seven patients the diastolic murmur was so characteristic on auscultation that the clinical diagnosis of aortic insufficiency was made. In only one of the remaining five patients were the diastolic vibrations accompanied by an audible diastolic murmur, and their significance remains obscure.

It is interesting to observe that in five of seven patients in whom diastolic vibrations were recorded from the precordium and dorsal spine, these vibrations differed markedly in configuration and were evidently produced by unrelated mechanisms.

PHONOCARDIOGRAMS ILLUSTRATING THESE OBSERVATIONS

The murmur recorded from the dorsal spine in Fig. 1 is characteristic of those found in coarctation of the aorta. The vibrations are crescendo-decrescendo in configuration, continuing into early diastole and becoming minimal before the onset of systole. The very loud murmur recorded over the precordium is slightly different in configuration in that it has a high intensity in early systole.

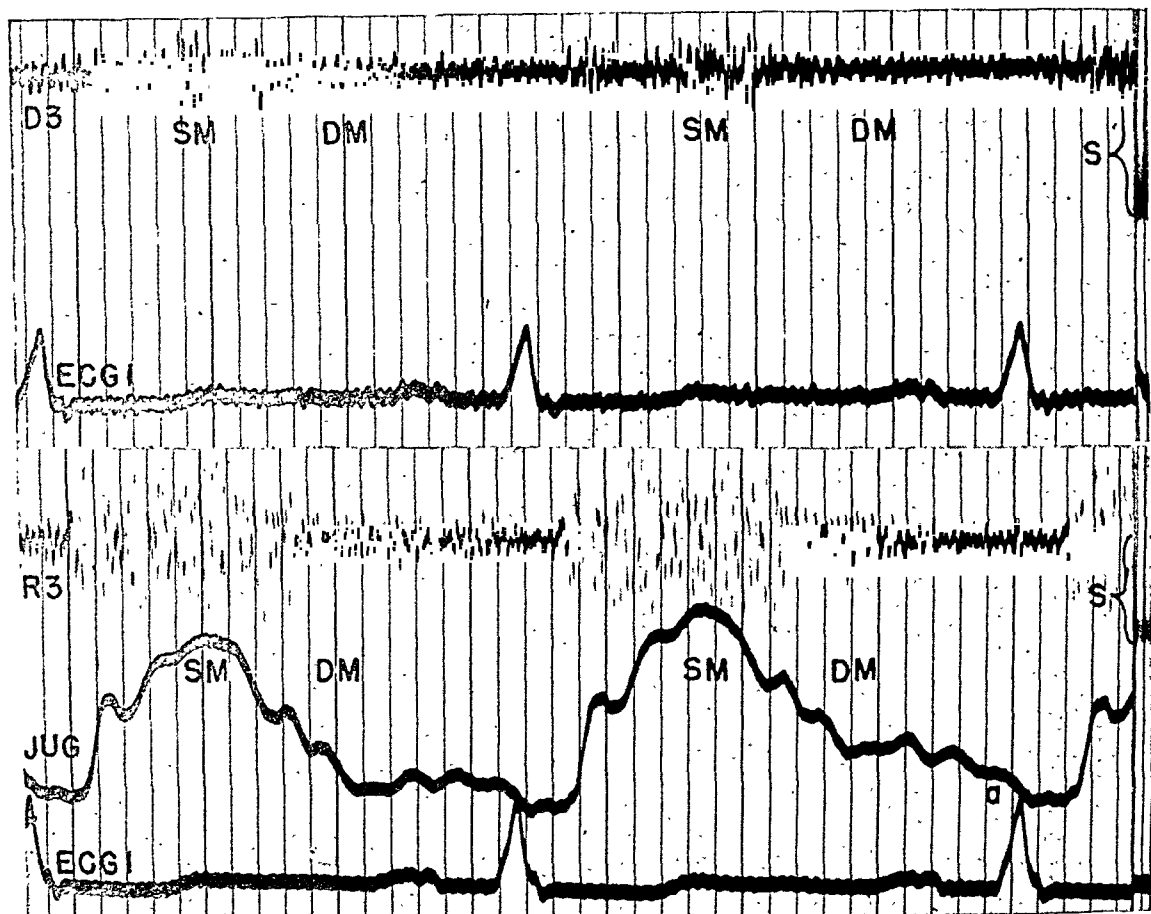


Fig. 1.—E. C., a 41-year-old man. Abnormality of heart discovered at age of 18. Hemoptyses of about 8 fluid ounces four times in last few years; recent dyspnea and palpitation. Grade 4 systolic murmur at apex; Grade 3 at base with Grade 3 diastolic murmur. At back both murmurs were heard, though less well. D3, Logarithmic microphone with large open bell over third dorsal spine; R3, logarithmic microphone with large open bell over third right intercostal space; Jug., jugular pulse; Ecg., Lead I.

Note the band "S" at the end of each tracing, representing the response of the instrument to a constant sound source of 500 cycles at 80 decibels above the threshold of audibility.

The first and second heart sounds are clearly recorded in the tracing from the dorsal spine in Fig. 2, where they are synchronous with the heart sounds recorded from the precordium. No diastolic murmur was heard in this patient, but the tracings demonstrate that the vibrations of the loud systolic murmur continue into early diastole in most cardiac cycles. The fact that the systolic murmur is of greater intensity over the back than over the precordium can be

demonstrated by relating the amplitude of the vibrations in each instance to that of the standard sound intensity which is shown immediately following each separate recording (see footnote to Fig. 1). This fact, together with the similarity of configuration of the two murmurs, would indicate that the systolic murmur in the back is conducted to the precordium.

Although no diastolic murmur was heard over the dorsal spine of the patient whose tracing is shown in Fig. 3, characteristic vibrations are recorded,

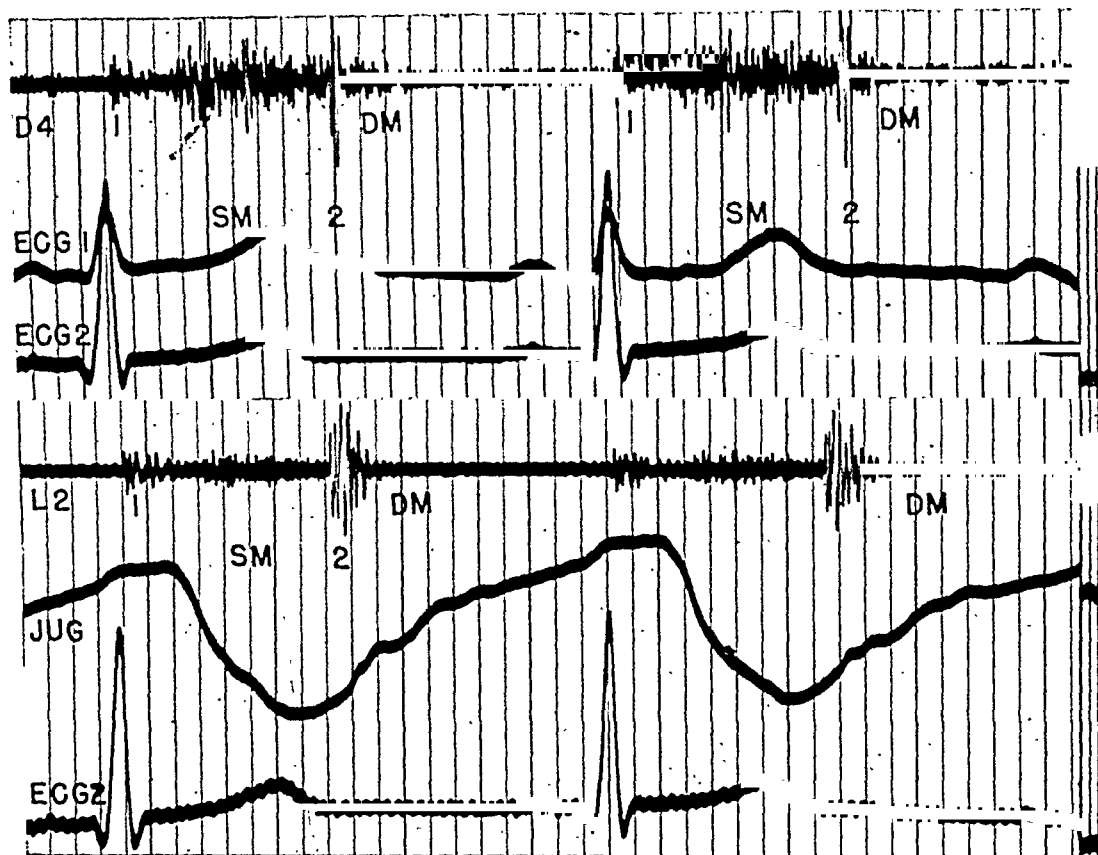


Fig. 2.—J. T., a 9-year-old boy. Abnormality of heart found at age 6. At age 7 blood pressure 152/86. Asymptomatic. Systolic murmur, Grade 3, along left sternal border and Grade 3 to 4 at fourth dorsal spine. No diastolic murmur. *D4*, logarithmic microphone with large open bell at fourth dorsal spine; *L2*, logarithmic microphone with large open bell over second left intercostal space; *Jug.*, jugular pulse; *Ecg.*, Leads I and II.

starting a considerable interval after the onset of systole and extending into early diastole. There is a louder murmur over the precordium, which is slightly shorter in duration and falls off in intensity before the second heart sound. Diastolic vibrations of decrescendo configuration are also recorded from the precordium, although in this location as well no diastolic murmur was audible. The reason that no diastolic murmur was audible in either location is probably that the systolic vibrations and second heart sound are of such intensity as to create a fatiguing effect on the human hearing mechanism which would persist into early diastole.

The characteristic systolic murmur over the dorsal spine, continuing in a decrescendo manner into early diastole, is very well shown in Fig. 4. The precordial tracing shows a systolic murmur of considerably lower intensity and different configuration. The diastolic murmur recorded over the left sternal border is crescendo-decrescendo and conforms to the pattern described in aortic or pulmonary insufficiency.⁶ This configuration therefore confirms the clinical impression that aortic insufficiency is present.

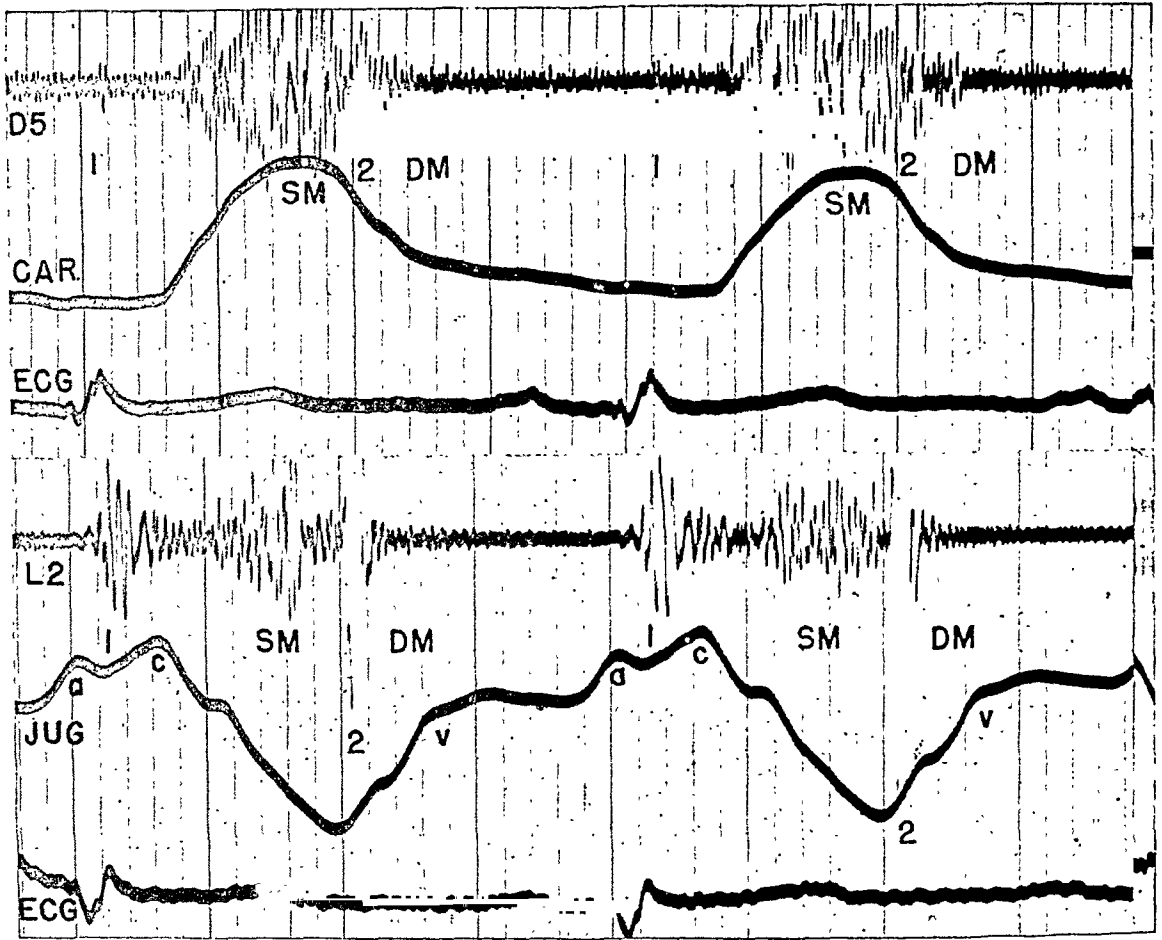


Fig. 3.—H. O., a 27-year-old woman. Congenital heart disease diagnosed at age of 10. Blood pressure 210/130. Systolic murmur, Grade 3, over second left intercostal space; Grade 2 over fifth dorsal spine. No diastolic murmur. D5, logarithmic microphone with large open bell over fifth dorsal spine; L2, logarithmic microphone with large open bell over second left intercostal space; Car., carotid pulse; Jug., jugular pulse; Ecg., Lead III.

ASYNCHRONISM OF FEMORAL AND RADIAL PULSES

Asynchronism of pulsation of the radial and femoral arteries, which was investigated and described by Lewis⁹ in 1933, has not been widely used in recent years as a diagnostic test. Lewis showed that in the normal patient the onset of the upstroke and the summit of the pulse wave are earlier in the femoral than in the radial artery, while in patients with coarctation of the aorta the re-

verse occurs. Synchronous pulse tracings are very easily and satisfactorily recorded on the Sanborn Tribeam phonocardiograph by the use of two of the capsules described by Miller and White.^{5,10} Illustrations of tracings taken in a patient with coarctation of the aorta and in a normal control subject are shown in Figs. 5 and 6. We believe that the demonstration of abnormal asynchronism constitutes a test which is of value in the diagnosis of coarctation of the aorta and should be more widely used.

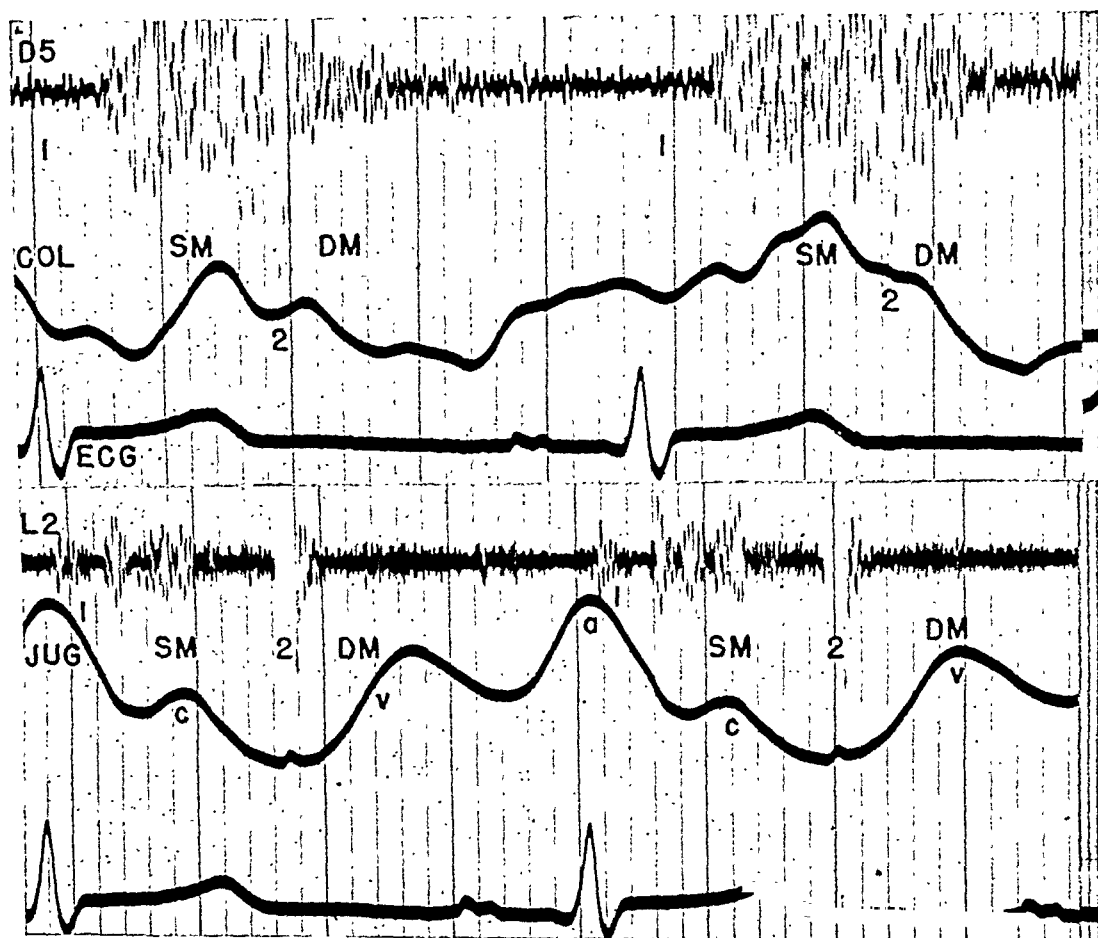


Fig. 4.—J. B., a 22-year-old man. Severe epistaxes over one month; otherwise asymptomatic. Heart enlarged. Grade 2 systolic and Grade 2 blowing diastolic murmurs over second left intercostal space. Grade 3 systolic murmur continuing into diastole at fifth dorsal spine. *D5*, logarithmic microphone with large open bell at fifth dorsal spine; *L2*, logarithmic microphone with Bowles diaphragm (0.015 inch thick) at second left intercostal space; *Col.*, pulse tracing from collateral channel over the back; *Jug.*, jugular pulse; *Ecg.*, Lead II.

SUMMARY AND CONCLUSIONS

1. Opinions differ as to which murmurs are characteristically present in uncomplicated coarctation of the aorta and which are due to concomitant defects.

2. In fifteen patients with coarctation of the aorta a systolic murmur was present over the dorsal spine in every case, and over the precordium in every case but one.

3. A diastolic murmur was present in six of these patients over the dorsal spine, and in five patients over the precordium.

4. Both systolic and diastolic murmurs are occasionally of greater intensity over the dorsal spine than over the precordium. Such a distribution of intensity is never present in the murmurs of isolated aortic valve deformity or patency of the ductus arteriosus, and in these fifteen patients there was no instance in which the murmurs were louder over the collateral vessels than over the dorsal

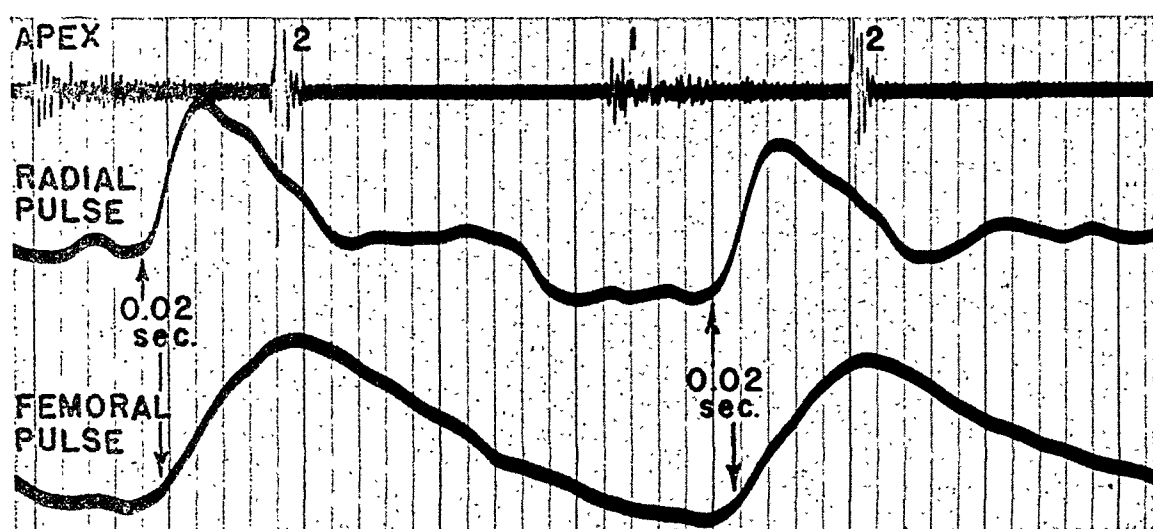


Fig. 5.—Synchronous tracings of femoral and radial pulses together with heart sounds in coarctation of aorta (Patient J. B.). (See also Fig. 4.)

Note that the onset of expansion is later in the femoral artery, which is characteristic of coarctation of aorta.

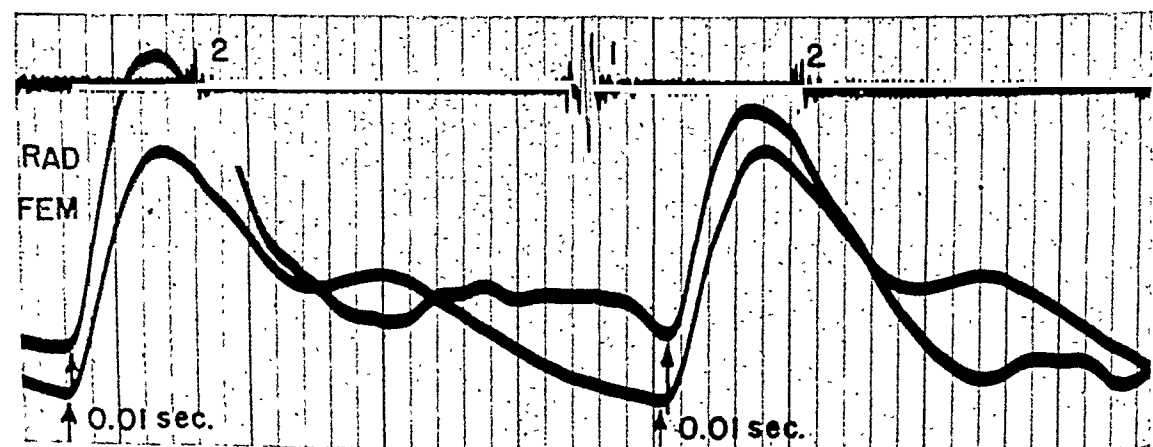


Fig. 6.—Synchronous femoral and radial pulse tracings in normal control subject, showing the femoral pulse preceding the radial pulse by 0.01 second.

spine. It is therefore probable that both systolic and diastolic murmurs are frequently present in uncomplicated coarctation of the aorta.

5. The method of study of the fifteen patients by phonocardiography is described, and the tracings obtained reveal the following facts: (a) Significant diastolic vibrations were present in tracings from the dorsal spine in every patient, although in only six of them was a diastolic murmur heard. The diastolic vibrations were characteristically of descrescendo configuration, being a continuation from the systolic murmur. (b) Diastolic vibrations from the precordium were recorded in ten patients, although a diastolic murmur was heard in only five of these. However, the vibrations were usually of different configuration from those recorded from the dorsal spine and were therefore caused by a different mechanism; in the majority of cases the configuration of these vibrations resembles that found in aortic insufficiency.

6. It is believed that systolic and diastolic vibrations from the dorsal spine are found on phonocardiography even more characteristically than they are heard on auscultation.

7. The reasons that diastolic vibrations may not be audible as a diastolic murmur are: (a) The intensity of a loud systolic murmur may be such as to cause a fatiguing effect on the human hearing mechanism which would mask the murmur in early diastole. (b) The frequent absence of the second heart sound on auscultation over the back may obscure the fact that the murmur extends into early diastole.

8. A satisfactory method for making synchronous records of the radial and femoral pulses is described. It is considered that the registration of abnormal asynchronism constitutes a test which is worthy of wider use in the diagnosis of coarctation of the aorta.

REFERENCES

1. Abbott, M. E.: Coarctation of the Aorta of the Adult Type. II. A Statistical Study and Historical Retrospect of 200 Recorded Cases With Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, *AM. HEART J.* 3:574, 1928.
2. Reifstein, G. H., Levine, S. A., and Gross, R. E.: Coarctation of the Aorta. A Review of 104 Autopsied Cases of the "Adult Type," Two Years of Age or Older, *AM. HEART J.* 33:146, 1947.
3. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund, p. 476.
4. Rappaport, M. B., and Sprague, H. B.: Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application. The Acoustic Stethoscope and Stethograph, *AM. HEART J.* 21:257, 1941.
5. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, *AM. HEART J.* 23:591, 1942.
6. Wells, B. G., Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of Basal Diastolic Murmurs, *AM. HEART J.* 37:586, 1949.
7. Rappaport, M. B., and Sprague, H. B.: The Standardization of the Intensity of Heart Sounds and Murmurs. In preparation.
8. Clark, R. J., and Ferminger, H.: Coarctation of the Aorta Associated With Stokes-Adams Syndrome, Complete Heart Block and Bicuspid Calcareous Aortic Valve, *New England J. Med.* 240:710, 1949.
9. Lewis, T.: Material Relating to Coarctation of the Aorta of the Adult Type, *Heart* 16:205, 1933.
10. Miller, A., and White, P. D.: Crystal Microphone for Pulse Wave Recording, *AM. HEART J.* 21:504, 1941.

INTERATRIAL SEPTAL DEFECT

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RECENT developments in the study of congenital heart disease have necessitated a more careful evaluation of clinical material. It is surprising that so few clinical studies of atrial septal defect comparable to that of Bedford, Papp, and Parkinson¹ are available in the literature. Our purpose is to describe the clinical and laboratory features in thirty-five cases of atrial septal defect and to evaluate the various diagnostic procedures at present available in the study of this, the most common lesion in congenital heart disease. The relative value and diagnostic significance of fluoroscopy, circulation times, angiocardiography, and venous catheterization will be discussed.

The material consists of sixteen unselected clinical cases collected during a period of eighteen months in a large cardiovascular clinic. On all patients adequate histories, physical examinations, fluoroscopy, and laboratory tests were available. Four of these cases came to necropsy. Another series of nineteen unselected autopsy cases was used to obtain further information on the pathology of this congenital lesion. In this particular series the clinical information was less detailed and is not included in our study.

HISTORICAL FEATURES

Not until 1934 was any attempt made to collect the available literature in a clinical analysis of cases. Roesler⁷ analyzed sixty-two cases, including one of his own. Shortly before this, McGinn and White³ had discussed the combination of interatrial septal defect and mitral stenosis. In 1938, Taussig, Harvey, and Follis⁴ reported four patients who came to necropsy and again emphasized the frequency of superimposed valvular disease, especially mitral stenosis, which in their cases, they considered to be caused by rheumatic fever. Recent interest in angiocardiography has added little to previous fluoroscopic studies. In reviewing ten cases, Steinberg, Grishman, and Sussman⁸ were able to supply important diagnostic information in only one case. Of greatest value have been the studies of right heart catheterization, such as those of Brannon, Weens, and Warren⁹ and those of Burwell and Dexter.¹⁰ The validity of the results and the diagnostic significance of the procedure will be discussed later. Finally, the

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With the technical assistance of Miss Mary Mayo.

Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

work of Hitzig¹¹ with circulation times has added another important contribution to the diagnostic armamentarium.

EMBRYOLOGY AND PATHOLOGY

The embryology and pathology of interatrial septal defect have been discussed by Bedford, Papp, and Parkinson.¹ They feel that (1) the clinical entity of atrial septal defect is a congenital malformation to be distinguished from simple probe patency of the foramen ovale; (2) it is the most frequent of all congenital cardiac malformations, constituting, as a single lesion, 7 to 25 per cent of all such cases; (3) it is almost always located at the fossa ovalis, and is due to defect in closure, involving the septum primum, the septum secundum, or the septum intermedium.

Two hypotheses concerning the dynamics of atrial septal defect might be mentioned. Schnitker,⁵ referring to Straub,⁶ has stated that left atrial pressure measured in the dog is significantly greater than right atrial pressure (a point in conformity with the mechanism of closure of the foramen ovale at birth) and that this mechanism may account for the left-to-right shunt. Uhley,¹² in refuting this mechanism, believes that the explanation is a simple hydrostatic one, and points to the more cephalad position of the left atrium. This gravitational effect should be considered and is a factor in the Bernouilli equation of energy of flow. Brannon⁹ states that "a satisfactory explanation of the left-right shunt has not been offered." His studies with venous catheterization have added significant information to this vexing problem. The apparent pressure difference between the left and right atrium varies from 2.0 to 4.0 millimeters of mercury. The arterial oxygen saturation of the right atrium does not appear to be affected by placing of the patient in the head down position. It would thus appear that the intrinsic difference in pressure between the left and right atria is the more adequate explanation of the left-to-right shunt in uncomplicated atrial septal defect. By cardiac catheterization the output of the right ventricle is found to be approximately twice that of the left ventricle, the left ventricular output being within the normal range. The post-mortem findings in nineteen cases of interatrial septal defect are summarized in Table I.

The findings in Table I conform in general with the previous pathologic concept of the interatrial septal defect. The findings in our series can be summarized as follows:

1. Enlargement of the right side of the heart was predominant.
2. The atrial septal defect was always over 1.0 cm. in diameter and averaged 2.0 to 7.0 centimeters.
3. The pulmonary-vascular system was always affected to some degree, usually with gross dilatation and often with moderate atherosclerosis of the pulmonary vessels.
4. The left side of the heart was often affected, in the absence of complicating lesions such as mitral stenosis or coarctation. When the left side of the heart was enlarged, it occurred along with enlargement of the right side. This

involvement of the left side of the heart is an unusual finding in conjunction with right side enlargement and may represent a situation similar to cor pulmonale; for example, there is very frequent left side involvement in the presence of hypertrophy of the right ventricle.

TABLE I. PATHOLOGIC FINDINGS IN NINETEEN CASES OF INTERATRIAL SEPTAL DEFECT STUDIED POST MORTEM

1. Average weight of heart	594.2 grams
2. Right atrium:	
Mildly dilated	3 patients
Moderately dilated	4 patients
Markedly dilated	5 patients
Unrecorded	7 patients
3. Left atrium:	
Mildly dilated	6 patients
Moderately dilated	3 patients
Markedly dilated	1 patient
Normal	1 patient
Unrecorded	8 patients
4. Average width of right ventricle	6.2 mm. (17 cases)
5. Average width of left ventricle	13.0 mm. (14 cases)
6. Average width of atrial septal defect	2.7 cm. (18 cases)
7. Average circumference of mitral valve (none with mitral stenosis)	11.2 cm. (14 adults)
8. Myocardium:	
Normal	7 patients
Infarct	4 patients
Unrecorded	8 patients
9. Evidence of moderate to marked arteriosclerosis:	5 patients
10. Average age at death	49 years
11. Causes of death:	
Unrecorded	4 patients
Heart failure	8 patients
Bacterial endocarditis, coronary embolism, myocardial infarction, cerebral throm- bosis, paroxysmal embolus, bronchial pneumonia, infarct with failure (each of these)	1 patient
12. Complications of atrial septal defect:	
Coarctation of aorta	2 patients
Subacute bacterial endocarditis	1 patient

5. Uncomplicated interatrial septal defect allows a life span of many decades. In this series the age average at death is strikingly high. The oldest patients were 78 to 80 years old.

6. The diagnosis of interatrial septal defect often appeared secondary to various types of degenerative heart disease.

CLINICAL FEATURES

Certain unusual aspects of interatrial septal defects distinguish this anomaly from other congenital cardiovascular abnormalities. The most significant of these are listed:

1. Interatrial septal defects appear more frequently in the female than in the male. In Roesler's⁷ series of sixty-two cases 61.7 per cent of the patients were female; in the fifty-two cases comprising the series of Bedford and associates,¹ 80 per cent were female; and in our own series 81 per cent of sixteen clinical cases and 58 per cent of nineteen autopsied patients were female. The explanation of this sex linkage is not clear. Medvei and Roesler¹⁵ speak of the hereditary tendency in the pathologic changes in cardiac development. Such marked sex linkage would seem to be more likely "genototypically conditioned," as Medvei and Roesler suggest, than the result of virus disease in the mother.¹⁴

2. The extreme rarity of subacute bacterial endocarditis has received frequent comment. In our single case the bacterial lesion was not present at the site of the defect. Bedford and his associates¹ state that the literature presents only one case in which the vegetation was present along the septal defect.

3. The absence of significant associated congenital abnormalities is a matter of some importance. Roesler's¹ series showed fifteen patients with associated congenital abnormalities, but only four of these (four cases of coarctation) appeared significant. In the ten autopsied cases in the series of Bedford and co-workers¹ ventricular septal defect was present once, slight coarctation once, and slight patency of the ductus arteriosus once. In our autopsy series, coarctation was present twice; in the clinical series, interventricular septal defect, bicuspid aortic valve with aortic regurgitation, coarctation, and patent ductus arteriosus were each present once.

4. The association of valvular heart disease has been frequently discussed. The mitral valve, involved in thirty of Roesler's⁷ sixty-two cases and in four of the ten autopsied cases of the series of Bedford and associates,¹ is the most frequently associated lesion, and is presumably of rheumatic origin. Clinical correlations of heart size, with and without mitral stenosis, tend to minimize the importance of the valvular defect in affecting chamber enlargement. Bedford,¹ stated: "The heart, on the whole, appeared to be more voluminous when mitral stenosis was present." From a purely clinical standpoint, the diagnosis of mitral stenosis is probably made less frequently than the lesion is present, because of the marked cardiac rotation inspired by the huge right ventricle. In our clinical series, a mitral diastolic murmur was heard twice.

PHYSICAL SIGNS

It has been repeatedly emphasized in previous clinical studies that no physical signs in atrial septal defect have real diagnostic significance. We have strongly suspected the diagnosis of atrial septal defect on two occasions prior to fluoroscopy. This has been on the basis of clinical signs alone, without

significant information concerning the presence of heart disease from birth, or other definite leads. We do not wish to imply that the diagnosis can be made without fluoroscopy, and it is certainly to be assumed that the factor of error in such "clinical suspicion" is quite large. The salient feature of this "clinical suspicion" is the evidence of right ventricular enlargement *without* the presence of mitral stenosis or other pathology responsible for right ventricular enlargement.

Our purpose in calling attention to the physical signs of marked right ventricular enlargement is similar to that of Roesler.⁷ We feel that it adds materially to the clinical appraisal and helps to differentiate other disease entities, such as primary pulmonary disease and constrictive pericarditis. It is pertinent here to quote Roesler,⁷ who has given so much attention to cardiac pulsations: "In enlargement of the right ventricle of considerable degree, but without hypertrophy, pulsatory heaving of the lower sternum occurs The systolic propulsion of the lower central portion of the thoracic wall is due partly to change in shape of the cardiac mass from a transverse ellipse in cross section to a cone, and partly to recoil. The latter factor is increased by high pressure in the pulmonary artery, and by increased filling of the right ventricle. As long as the left ventricle is not displaced, a normal circumscribed apical thrust may persist. In the presence of considerable enlargement of the right ventricle, the front wall of the heart is mainly formed by it, and so is the apical thrust, the left ventricle having been pushed away from the wall of the chest. This finding of a well-circumscribed resistant thrust in the apical region in the presence of a predominant and enormous right-sided enlargement, is not known for any other clinicopathologic condition than atrial septal defect."

The physical signs, therefore, are the physical signs associated with right ventricular hypertrophy, and are listed in Table II.

Precordial bulge, displacement of the apex beat, mitral and pulmonic murmurs, accentuation of the pulmonic second sounds, and so forth, are all manifestations of isolated right ventricular hypertrophy. The mitral diastolic murmur alone is the physical sign of significance in the differentiation of pure atrial septal defect from Lutembacher's syndrome.

Much controversy has arisen concerning the relationship of heart size to the presence or absence of murmurs. It is certainly true that no murmurs may be present with considerable right-sided enlargement (two of the cases with necropsy proof in the series of Bedford, Papp, and Parkinson¹). It is also quite definite that small defects, asymptomatic, without evidence of cardiac hypertrophy, and with only a prominent bulge in the region of the pulmonary conus, may constitute a "subclinical" group of patients. Little exact information is available in this group. As a general rule, however, there is some relationship between the loudness of the pulmonic murmurs, the presence of a systolic thrill, and the presence of a pulmonic diastolic murmur to the heart size and general condition of the patient. According to Thompson,¹³ a prominent pulmonic systolic murmur is a rather late clinical sign, and the presence of a thrill or diastolic murmur is in general associated with huge defects and considerable

cardiac enlargement. The murmur is due to dynamic factors within the pulmonary artery and not to the atrial septal defect itself.

TABLE II. SYMPTOMS AND SIGNS IN SIXTEEN CLINICAL CASES OF ATRIAL SEPTAL DEFECT (AVERAGE AGE, 23 YEARS)

	Cases
A. <i>Symptoms</i>	
1. Shortness of breath	9
2. Palpitations	4
3. Hemoptysis	4
4. History of heart failure	3
5. "Pneumonitis"	3
6. Substernal pain	2
7. "Arthritis"	1
B. <i>Signs</i>	
1. Cyanosis	7
2. Clubbing	1
3. Increased second pulmonic sound	6
4. Pulmonic systolic thrill	2
5. Pulmonic systolic murmur, marked	4
Pulmonic systolic murmur, moderate	8
Pulmonic systolic murmur, mild	2
Pulmonic systolic murmur, none	2
6. Pulmonic diastolic murmur	7
7. Mitral systolic murmur	3
8. Mitral diastolic murmur	1
9. Mitral systolic and diastolic murmurs	1
10. Right heart failure	4

RADIOLOGIC FEATURES

From what has been previously stated, it is apparent that the presumptive diagnosis of atrial septal defect depends upon radiologic diagnosis. The "clinical suspicion" referred to earlier becomes almost a certainty following the adequate demonstration of gross, isolated, right-sided cardiac enlargement, together with large central pulmonary arteries, with or without obvious pulsations. However, the so-called hilar dance, or obvious pulsations of the large pulmonary arteries, aids greatly in establishing a presumptive diagnosis. In no other condition is the evidence of enlargement of the pulmonary arterial bed more dramatic. The characteristic roentgenologic features follow:

I. *In the Anteroposterior Position.*—

A. Enlargement of the heart chiefly to the left, *produced by enlargement of the right ventricle.*

B. Prominence and elongation of the pulmonary arc. This is usually the case with small defects. With large defects, extreme, almost aneurysmal bulging of the pulmonary arc is typical.

C. Enlargement of the heart to the right is unusual. Rarely enlargement to the right may be more pronounced than to the left (six of the cases of Bedford and associates¹).

D. The right pulmonary artery forms a large, dense, well-defined, almost comma-shaped shadow in the right hilar region. The left pulmonary artery occasionally protrudes beyond the pulmonary arc, forming a double contour.¹⁶

E. Pulmonary congestion in the periphery and hydrothorax is conspicuous by its absence, even in the presence of congestive failure. Quite typical is the contrast between the radiant peripheral lung fields and the dense agglomeration of hilar shadows.

F. Pulsation of the hilar pulmonary arteries is often seen (hilar dance). We have found this more definite and frequent in the right hilar region, presumably because of the ease with which the vessels near to the heart are seen.

II. *In the Right Oblique Position.*—

A. Enlarged pulmonary conus and pulmonary artery. There is increased width of the heart shadow in its upper one-third.

B. Visualization of the right pulmonary artery as an oval pulsating mass in front of the aorta, and just above the right bronchus. This is seen so easily since its density is due to the "end on" view of the right pulmonary artery. It is the "pulmonal fleck" as described by Schwedel and Epstein.²

C. Posterior displacement of the esophagus by the enlarged pulmonary vessels.

D. Occasional budge in the region of the left atrium. In the series of Bedford and associates,¹ four showed slight left atrial enlargement fluoroscopically, and of these only one patient had clinical mitral stenosis.

III. *In the Left Oblique Position.*—

A. The position of the left branch of the pulmonary artery, crossing and obscuring the pulmonary window, is important.

B. The left ventricle is of normal size. The right ventricle may present a prominent bulge or "auricular shelf."

A summary of the x-ray findings in twelve of our clinical cases is shown in Table III.

CIRCULATION TIMES

A presumptive diagnosis of atrial septal defect, such as that afforded by the typical fluoroscopic picture, is not entirely satisfying. The picture may be simulated by primary pulmonary hyperplasia, by rare cases of thyrotoxicosis, or by the tetralogy of Eisenmenger. The proof of an intracardiac shunt should be secured. A method of achieving this aim is by the use of circulation times, as recently reviewed by Hitzig.¹¹ The short-circuiting of ether from right to left, without its passing through the lungs, caused peculiar paresthesiae in the face,

TABLE III. X-RAY FINDINGS IN TWELVE CLINICAL CASES OF ATRIAL SEPTAL DEFECT

1. Cardiac enlargement:		10 (Recorded)
Slight	6	
Moderate	2	
Marked	2	
Predominant enlargement to left	8	
Enlargement to right and to left	2	
2. Pulmonary conus abnormal:		12
Markedly enlarged	8	
Moderately enlarged	2	
Slightly enlarged	2	
Hilar dance	7 (of 12)	
3. Pulsating right pulmonary artery in right oblique position		3

arms, and legs, which is often wavelike in character. In atrial septal defect it has been shown that the arm-to-lung ether time and the arm-to-face ether time (paresthesia) are similar. The Decholin or saccharin times are not disturbed, except in the presence of mitral stenosis. The following times are taken from Hitzig¹¹ to illustrate this point:

	SACCHARIN (ARM-TO-TONGUE)	(ETHER ARM-TO-FACE)	ETHER (ARM-TO-LUNG)
Interatrial septal defect	17.5	8.0	8.5
Lutembacher's syndrome	22.0	8.5	8.5

The ability of circulation times to rule out interatrial septal defect has not yet been clinically confirmed. When the test is positive, it adds greatly to the strength of the diagnosis. In all probability, a negative result is not of great significance.

CARDIAC ANGIOGRAPHY

Of little value is cardiac angiography. Steinberg, Grishman, and Sussman⁸ were able to demonstrate the defect only once in ten attempts. It should be shown that the left atrium becomes opaque at the time of right atrial filling. It is apparent that this can be accomplished only when there is a temporary and artificial reversal of flow, and the Diodrast is directed into the heart under pressure. As mentioned by these authors, revisualization of the right atrium following filling of the left heart chambers would probably be quite inconclusive, as a result of the marked dilution which would occur.

CARDIAC CATHETERIZATION

The most reliable diagnosis of interatrial septal defect is achieved by the cardiac catheter.⁹ Positive proof of the interatrial septal defect may be secured by passing the catheter from the right atrium into the left atrium. Any septal

defect sufficiently large to permit passage of the catheter would probably represent a clinically significant interatrial septal defect. This procedure has been accomplished by Brannon, Weens, and Warren⁹ in one case and by ourselves in one case. The position of the catheter in the left atrium is confirmed by the obtaining of fully oxygenated blood, the oxygen content of which is similar to that of femoral artery blood. To increase the certainty of the diagnosis, pressure tracings in this position should conform to routine atrial pressure curves. If one is unable to pass the catheter into the left atrium, a presumptive diagnosis of interatrial septal defect may be made by showing a definite increase in the oxygen content of the blood of the right atrium over that of the blood of the superior vena cava. According to Burwell and Dexter,¹⁰ the greatest normal variation in the blood oxygen content between the superior vena cava and the right atrium is 1.9 volumes per cent. In the three cases reported by Brannon, Weens, and Warren,⁹ the oxygen content of the blood from the right atrium averaged 14.2 volumes per cent, with an average of 11.3 volumes per cent and 11.6 volumes per cent for blood from the superior vena cava and inferior vena cava, respectively. Thus, if the oxygen content of the blood from the right atrium is 2 or more volumes per cent greater than that from the superior vena cava, a presumptive diagnosis of interatrial septal defect may be made; the diagnosis is presumptive because anomalous pulmonary veins emptying into the right atrium could cause a similar result. To our knowledge, catheterization of the pulmonary veins entering in either the right or left atrium has not thus far been accomplished.*

In summary, the most positive diagnosis of interatrial septal defect is made by (1) the passage of the catheter from the right into the left atrium, (2) the withdrawal of fully oxygenated blood in this position, (3) the simultaneous recording of pressure curves from right and left atria with a double lumen catheter. These curves should fit the routine atrial pattern, but left atrial pressure will be appreciably higher than right. The presumptive diagnosis of interatrial septal defect is made by the finding of increased oxygenation of right atrial blood. The oxygen content of the right atrial blood should be 2 volumes per cent or more than that of the superior vena cava.

CONCLUSIONS

1. An analysis has been made of thirty-five cases of interatrial septal defect. Sixteen were studied clinically and nineteen post mortem. Autopsy confirmation was secured in four of the cases studied clinically.

2. The diagnostic criteria of interatrial septal defect have been analyzed and the following general statements may be made:

- A. The symptomatology in interatrial septal defect is not distinctive, the most common presenting complaints being fatigue and shortness of breath.

- B. Physical examination may point to the presence of right ventricular hypertrophy, which in the absence of mitral stenosis, particularly in a young individual, is suggestive of interatrial septal defect.

*The authors have found the catheter in transposed pulmonary veins entering the right atrium in a case of tricuspid atresia.

C. Adequate fluoroscopy should demonstrate right ventricular hypertrophy and pulmonary hypertension, and should eliminate most conditions to be considered in the differential diagnosis. Abnormal and uniform enlargement of the large pulmonary arterial trunks with or without hilar dance is a necessary feature of the fluoroscopic pattern. Even after adequate fluoroscopy, however, certain conditions such as pulmonary hyperplasia, high ventricular septal defect with gross enlargement of the pulmonary artery, or Eisenmenger's complex, may simulate interatrial septal defect.

D. Circulation times occasionally are of value in showing the presence of a right-to-left shunt.

E. Angiocardiography is of little if any value in the diagnosis.

F. Cardiac catheterization may give information of much diagnostic value. A presumptive diagnosis of interatrial septal defect is established by the finding of increased oxygenation of right atrial blood. A positive diagnosis of interatrial septal defect is made by the passage of the catheter through the septal defect. Confirmation of its position in the left atrium may be obtained by fluoroscopy and film and by the withdrawal of fully oxygenated blood, along with the simultaneous registration of a typical atrial pressure curve.

REFERENCES

1. Bedford, D. E., Papp, C., and Parkinson, J.: Atrial Septal Defect, *Brit. Heart J.* 3:37, 1941.
2. Schwedel, J. B., and Epstein, B. S.: Radiological Study of Pulmonary Artery With Special Reference to the Main Branches, *AM. HEART J.* 11:292, 1936.
3. McGinn, S., and White, P. D.: Interauricular Septal Defect Associated With Mitral Stenosis, *AM. HEART J.* 9:1, 1933.
4. Taussig, H. B., Harvey, A. M., and Follis, R. H.: The Clinical and Pathological Findings in Interatrial Septal Defects. A Report of Four Cases, *Bull. Johns Hopkins Hosp.* 63:61, 1938.
5. Schnitker, M. A.: The Electrocardiogram in Congenital Heart Disease, Cambridge, Mass., 1940. Harvard University Press.
6. Straub, H., Bethe, A., and Bergman, G.: *Handbuch der normalen und Pathologischen Physiologie*, Berlin, 1926, J. Springer, 7, p. 230 (Part I).
7. Roesler, H.: Interatrial Septal Defect, *Arch. Int. Med.* 54:339, 1934.
8. Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. II. Intracardiac Shunts, *Am. J. Roentgenol.* 49:766, 1943.
9. Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial Septal Defect, *Am. J. M. Sc.* 210:480, 1945.
10. Burwell, C. S., and Dexter, L.: Venous Catheterization in Congenital Heart Disease, *Mod. Concepts Cardiovas. Dis.*, April, 1947.
11. Hitzing, W. M.: The Value of Circulation Times, *Mod. Concepts Cardiovas. Dis.* August, 1947.
12. Uhley, M. H.: Lutembacher's Syndrome, and a New Concept of the Dynamics of Interatrial Septal Defect, *AM. HEART J.* 24:315, 1942.
13. Thompson, W. P.: Personal communication.
14. Swan, G., and Tostevin, A. L.: Congenital Abnormalities in Infants Following Infectious Disease During Pregnancy, With Special References to Rubella, *M. J. Australia* 1:645, 1946.
15. Medvei, C. V., and Roesler, H.: Zur Erbbiologie angeborener Herzfehler, *Ztschr. f. klin. Med.* 119:527, 1932.

RELATIONSHIP BETWEEN THE REDUCTION IN CORONARY FLOW AND THE APPEARANCE OF ELECTRO-CARDIOGRAPHIC CHANGES

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ALTERATIONS of the electrocardiogram characterized by displacement of the RS-T segment and modification in the shape of the T wave were first ascribed to myocardial infarction by Pardee.¹ Subsequent experimental work^{2,3,4} showed that electrocardiographic changes of the same type can be reproduced in the dog by complete occlusion of a coronary artery of very brief duration and that such changes disappear immediately after release of the occlusion. Since all previous investigations have been limited to the effect of the complete occlusion of a coronary artery, it consequently seemed of interest to study the relationship between the reduction of coronary flow produced by partial occlusion of a coronary artery and the appearance of electrocardiographic changes.

METHOD

Eleven dogs weighing from 12 to 23 kilograms were used. They were given subcutaneously 2.0 c.c. of a 2 per cent solution of morphine sulfate. Then they received intravenously 1.25 c.c. to 1.5 c.c. per kilogram of body weight of a 20 per cent solution of sodium barbital. Under artificial respiration, the chest was opened through a midsternal incision and the heart suspended in a pericardial cradle. The blood was rendered incoagulable by the intravenous administration of an initial dose of 5.0 mg. of heparin per kilogram, then 3.0 mg. per kilogram every half hour. A segment of the left anterior descending coronary artery was dissected. A cannula was introduced into the distal segment and the distal end of the proximal segment closed (Fig. 1). The mean coronary blood flow was measured and recorded with an electromagnetic rotameter.^{5,6} A cannula was inserted in the left common carotid artery; in some experiments, it was introduced down to the root of the aorta in the neighborhood of the coronary ostia. As shown in Fig. 1, when the screw clamps placed in *E* and *G* were open and the screw clamp placed in *F* was closed, the blood was allowed to flow via the carotid cannula (*A*) through the flowmeter (*B*) into the cannulated coronary artery (*C*). When the screw clamps *E* and *G* were closed and the clamp *F* was open, the blood flowed from the carotid cannula (*A*) via the short circuit into the

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Supported by a grant from the Life Insurance Medical Research Fund, Inc.

Presented at the Twenty-First Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

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cannulated coronary artery (*C*). In this manner, a zero flow was recorded without producing myocardial ischemia. The screw clamp in *E* was also used to reduce temporarily the coronary flow to the desired level. An optical manometer of the Gregg type (*D*) was used to record the mean arterial blood pressure. The flowmeter had been previously calibrated, according to the technique of Shipley and Crittenden,^{5,6} with liquids of viscosities covering the range of viscosities of the dog blood in such acute experiments. Numerous determinations of the viscosity of the blood were done during each experiment. Unipolar electrocardiograms were recorded. The indifferent electrode made of German silver was placed under the skin of the dog's left leg and the exploring electrode in the center of the area irrigated via the cannulated coronary artery. The exploring electrode, a nonpolarizable silver-silver chloride electrode, was placed directly on the epicardium, or hooked under the epicardium, or, as in most experiments, hooked in a gauze pad applied on the epicardium and impregnated with physiologic saline solution. Blood pressure and coronary blood flow were recorded continuously throughout the experiments. After one and generally several electrocardiograms were recorded, the blood flow of the coronary artery was reduced to the desired level by means of the screw clamp, *E* (Fig. 1) and maintained at that level by adjustment of the clamp. During and after the occlusion, electrocardiographic tracings were recorded at one-half to one-minute

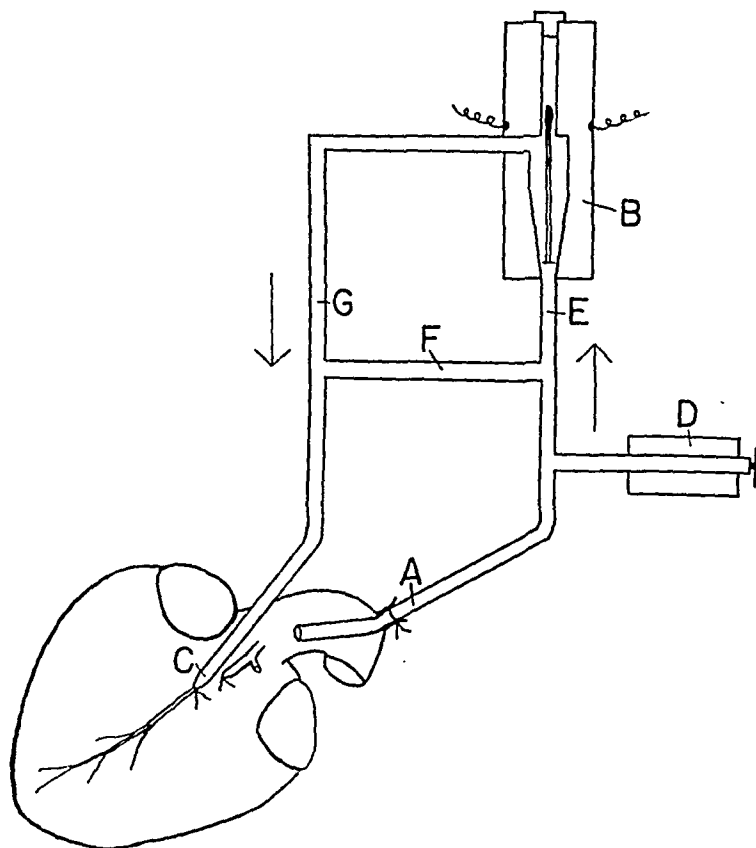


Fig. 1.—Schema of the apparatus used to measure and record the mean arterial blood pressure in the aorta and the mean coronary blood flow in the left anterior descending coronary artery.

intervals. The occlusion was maintained for five minutes in most experiments; in a few experiments, the occlusion lasted three, ten, and fifteen minutes (Table I). In most dogs, several partial or complete occlusions were performed. A period of recovery was always allowed between two successive occlusions.

TABLE I. SUMMARY OF EXPERIMENTS PERFORMED

NUMBER OF EXPERIMENT	DIMINUTION OF CORONARY FLOW (PER CENT)	DURATION OF OCCLUSION (MINUTES)	T-WAVE CHANGE	RS-T SEGMENT CHANGE	DOG
1	10	5	None	None	A
2	10	5	None	None	D
3	12	5	None	None	C
4	17	15	None	None	E
5	18	5	None	None	D
6	20	10	None	None	F
7	23	5	None	None	F
8	25	5	None	None	C
9	25	10	None	None	E
10	29	5	None	None	B
11	29	5	None	None	D
12	29	5	Slight	Slight	D
13	31	5	None	None	G
14	33	5	None	None	E
15	36	5	None	None	I
16	36	5	None	None	K
17	37	5	Slight	Slight	A
18	37	5	Marked	Slight	D
19	42	5	None	None	E
20	43	5	Slight	Slight	C
21	44	5	Slight	None	F
22	44	5	Slight	Slight	H
23	45	5	Slight	None	C
24	48	5	None	None	G
25	49	5	Slight	None	G
26	50	5	Slight	Slight	C
27	50	5	Marked	Slight	C
28	50	5	Marked	Marked	A
29	52	5	Slight	Slight	J
30	56	5	None	None	K
31	57	5	Slight	Slight	K
32	58	5	Slight	None	I
33	58	5	Marked	Marked	D
34	60	5	Slight	None	H
35	61	5	Marked	Slight	E
36	67	5	Marked	Marked	H
37	69	5	Slight	None	I
38	71	5	Marked	Marked	D
39	78	5	Marked	Marked	H
40	79	5	Marked	Marked	G
41	80	5	Marked	Marked	G
42	82	5	Marked	Marked	G
43	85	5	Marked	Marked	K
44	86	5	Marked	Marked	K
45	88	5	Marked	Marked	I
46	89	5	Marked	Marked	I
47	100	3	Marked	Marked	D
48	100	3	Marked	Marked	E
49	100	5	Marked	Marked	G
50	100	5	Marked	Marked	H
51	100	3	Marked	Marked	J

RESULTS

Fig. 2 shows the records of mean arterial blood pressure and flow through the cannulated coronary artery during a typical experiment. During the control period, the mean coronary blood flow ranged between 25 and 18 c.c. per minute and the mean arterial blood pressure oscillated between 120 and 105 mm. of mercury. At the first arrow, the flow through the cannulated coronary artery was reduced by means of the screw clamp. It varied between 11.0 and 8.5 c.c. per minute for five minutes. The blood pressure did not change. At the second arrow, the screw clamp was released. The blood pressure did not change, but the coronary flow rose to a maximum of 39 c.c. per minute, a level higher than the control value, then decreased progressively toward the control value. Such an increase of coronary flow without any change in blood pressure after a partial coronary occlusion has been described previously after temporary complete coronary occlusion.⁷ It may be pointed out that such a secondary rise in coronary flow was often observed in our series of experiments after a partial coronary occlusion that was not marked enough to produce any electrocardiographic change.

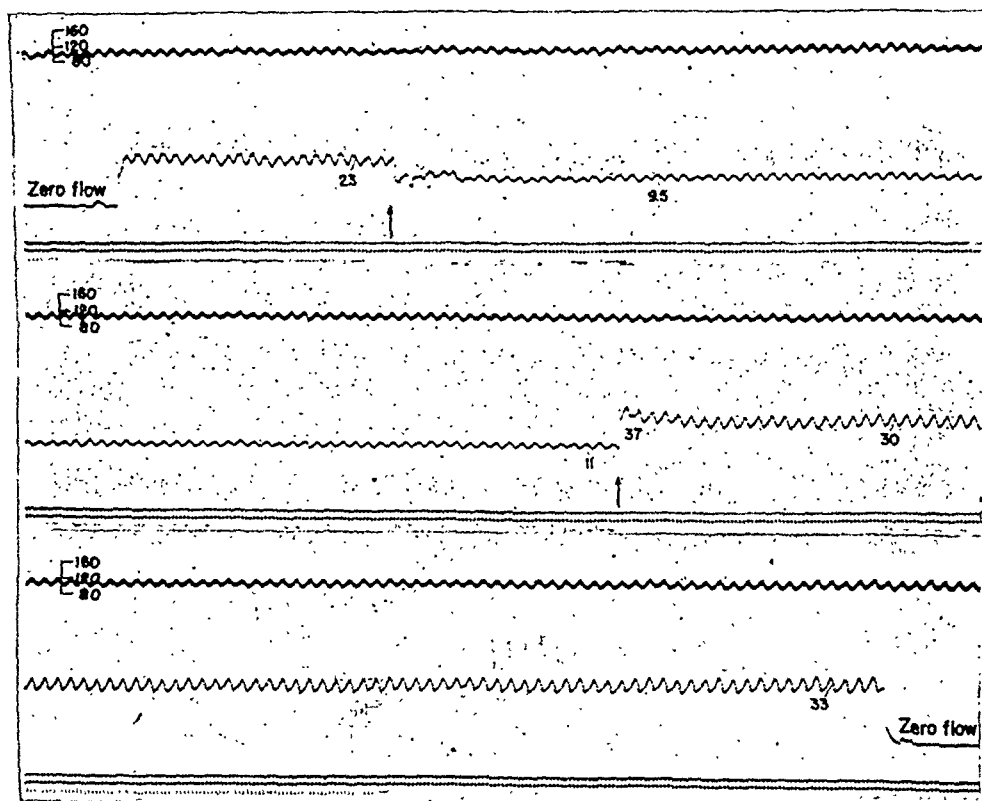


Fig. 2.—Continuous record of the mean arterial blood pressure (upper tracing) and mean coronary blood flow (lower tracing) in a typical experiment.

Scale for the blood pressure in millimeters of mercury. Values for the coronary blood flow in cubic centimeters per minute. At first arrow, partial occlusion initiated; at second arrow, occlusion released. Time in seconds.

Fig. 3 illustrates the electrocardiographic changes observed during a temporary partial occlusion. Tracing *A* is a normal electrocardiogram. In our experiments the T wave of the control electrocardiogram was always inverted. Tracing *B* is the tracing recorded after two minutes of a partial occlusion during which the blood flow was reduced by 78 per cent of its control value (from a control value of 9.0 c.c. per minute to 2.0 c.c. per minute). As can be seen, the T wave is less deeply inverted and the RS-T segment is elevated. Changes of the RS-T segment and T wave of such a degree were termed "slight." Tracing *C* was recorded after three minutes of occlusion. The RS-T segment is more elevated and the T wave less deeply inverted. Changes of the RS-T segment and T wave of such a magnitude were termed "marked." The electrocardiogram was the same after five minutes of occlusion. It must be added that the changes were not sudden but progressive. Tracing *C* also shows a marked degree of electrical alternation, a phenomenon not constantly but frequently observed in our experiments. After the release of the occlusion, the electrocardiographic changes disappeared progressively and the electrocardiogram became entirely similar to the control tracing after four minutes.



Fig. 3.—Unipolar electrocardiogram recorded from the region of the left ventricle irrigated via the cannulated coronary artery. *A*, Before the occlusion. *B*, After two minutes of partial occlusion during which the blood flow was reduced by 78 per cent of its control value (from 9.0 c.c. per minute to 2.0 c.c. per minute). *C*, After three minutes of the same occlusion. Tracing *B* illustrates changes of the RS-T segment and T wave that are called "slight changes" and *C* illustrates "marked changes" of the RS-T segment and T wave.

As seen in Table I, fifty-one transient partial or complete occlusions of the anterior descending coronary artery were produced in eleven dogs.

In sixteen partial occlusions on nine different dogs in which the blood flow was reduced from 10 to 36 per cent of its control value for a duration of five minutes, no electrocardiographic changes were observed except in Experiment 12, in which there was a slight change in the RS-T segment and T wave. In Experiments 4, 6, and 9, no electrocardiographic changes were observed, although the occlusions lasted fifteen, ten, and ten minutes, respectively.

In twenty-one partial occlusions on ten different dogs in which the reduction in coronary flow amounted to from 37 to 69 per cent of the original flow and was maintained for five minutes, the electrocardiographic changes were variable. Only occasionally was there no change (Experiments 19 and 30). Occasionally there was marked change in both the RS-T segment and T wave (Experiments 28, 33, and 36). In most occlusions, the changes in both the RS-T segment and T wave were slight.

In eleven occlusions on five different dogs in which the coronary blood flow was reduced by 71 to 100 per cent of its control value for a duration of five minutes, the changes in both the RS-T segment and T wave were always marked. The same held true in three more complete occlusions (Experiments 47, 48, and 51) in three dogs which lasted only three minutes.

When the occlusion led to electrocardiographic changes, minimal changes first appeared within about one minute of occlusion and became progressively more pronounced. The changes reached a maximum within three to five minutes of occlusion. Whether more prolonged occlusions would have increased further the degree of electrocardiographic changes was not determined. It seemed that the first change to appear after occlusion was the T-wave change. However, one must remember that T-wave changes are more easily noticed and measured because they are greater than the changes in the RS-T segment, and, therefore, such an observation may be more apparent than real. In all the occlusions done while the dog was in good condition, as gauged by the blood pressure and the coronary blood flow, the electrocardiographic changes produced by partial or complete occlusions of five minutes' duration were completely reversible. The electrocardiographic changes disappeared within three to five minutes after the termination of the occlusion. Under the experimental conditions described, coronary occlusion did not modify the mean arterial blood pressure.

After the release of partial as well as complete occlusion, the coronary flow increased above its control value. This increase was seen to occur even after occlusions that were too slight to produce electrocardiographic changes. It was also observed that the electrocardiographic changes often disappeared before the coronary flow had reverted to its control level.

CONCLUSIONS ·

An attempt was made to correlate the reduction of coronary blood flow and the appearance of electrocardiographic changes in anesthetized dogs by

measuring the experimentally produced changes in blood flow through a cannulated coronary artery and recording simultaneously the electrocardiogram from the ischemic area of the ventricular myocardium.

A reduction of blood flow of 10 to 35 per cent did not, as a rule, produce any electrocardiographic changes. With a reduction of 35 to 70 per cent, generally "slight" electrocardiographic changes in both the RS-T segment and T wave appeared. Occasionally no change was seen and sometimes the RS-T segment and T-wave changes were marked. With a reduction of 70 to 100 per cent, the changes were always marked.

When electrocardiographic changes were produced by the occlusion, minimal changes appeared within about one minute. These increased progressively in intensity and reached their maximum within three to five minutes. These electrocardiographic changes were reversible and disappeared completely within three to five minutes after release of the occlusion. The effect of longer periods of occlusion was not studied.

A partial occlusion may be too slight to produce electrocardiographic changes, although it may be sufficiently marked to lead to myocardial ischemia as it is shown by the increase of the flow through the cannulated coronary artery above its control value following the release of the occlusion. The electrocardiographic changes generally disappeared before the coronary blood flow had reverted to its control value.

REFERENCES

1. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26:244, 1920.
2. Wood, F. C., and Wolferth, C. C.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* 47:339, 1931.
3. Bailey, R. H., LaDue, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, *AM. HEART J.* 27:164, 1944.
4. Bailey, R. H., LaDue, J. S., and York, D. J.: Further Observations on the Ischemia-Injury Pattern Produced in the Dog by Temporary Occlusion of a Coronary Artery. Incomplete T Diversion Patterns, Theophylline T Reversion, and Theophylline Conversion of the Negative T Pattern, *AM. HEART J.* 27:657, 1944.
5. Shipley, R. E., and Crittenden, E. C., Jr.: An Optical Recording Rotameter for Measuring Blood Flow, *Proc. Soc. Exper. Biol. & Med.* 56:103, 1944.
6. Crittenden, E. C., Jr., and Shipley, R. E.: An Electronic Recording Flowmeter, *Rev. Scient. Instruments* 15:343, 1944.
7. Green, H. D., and Wégria, R.: Effects of Asphyxia, Anoxia and Myocardial Ischemia on the Coronary Blood Flow, *Am. J. Physiol.* 135:271, 1942.

OBSERVATIONS ON THE POTENTIAL VARIATIONS OF THE CAVITIES OF THE RIGHT SIDE OF THE HUMAN HEART

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IN 1934 Wilson, Johnston, and Hill¹ published observations on the potential variations of the ventricular cavities of the dog's heart and emphasized the bearing of their observations upon the interpretation of the QRS deflections of bipolar epicardial leads. The methods described and the principles laid down in their article were used later in the analysis of the precordial electrocardiogram² and have placed electrocardiographic interpretation upon a sounder and more logical basis. With the introduction of catheterization³ of the human heart it became possible to duplicate many of the observations made in the animal experiments referred to, and also to record the potential variations of the right auricular and right ventricular cavities in various types of cardiac abnormality which do not occur spontaneously in animals and cannot be simulated in experiments.

The first report dealing with intracavitary potential variations in man was made by Hecht⁴ in 1946. He concluded that the principles based on animal experiments could be applied safely to the interpretation of the human electrocardiogram. In the following year Battro and Bidoggia⁵ studied twelve normal subjects and eleven patients with cardiac abnormalities. They pointed out the resemblance of the tracings obtained from the cavity of the right auricle to those recorded from the auricular levels of the esophagus. In their normal subjects, leads from the right ventricle displayed a small initial R wave, followed by a large S and a negative T deflection. In a case of right bundle branch block the cavity of the right ventricle was initially positive, whereas in one of left bundle branch block it was negative throughout the QRS interval. Shortly after this report appeared, Sodi-Pallares and associates⁶ published similar observations on six normal subjects, on twenty patients with heart disease, and on dogs studied under various experimental conditions. They found a great similarity between the records obtained in human bundle branch block and those obtained in dogs in which right or left bundle branch block had been produced experimentally. In their normal subjects, leads from the right ventricular cavity yielded curves similar to those described by other workers. With respect to the ventricular

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Much of the work upon which this article is based was done with the aid of grants to Dr. Frank N. Wilson from the Horace H. Rackham School of Graduate Studies and the S. S. Kresge Foundation, and in part by a grant from the United States Public Health Service.

*Aided by a Fellowship from the Dazian Foundation for Medical Research.

complexes of these leads, patients with right ventricular hypertrophy did not differ significantly from normal subjects; those with left ventricular hypertrophy differed only in that the direction of the T wave was upward.

The purpose of our own studies has been to confirm and extend the observations published by others, and in particular to compare the potential variations of the cavity of the right ventricle with those of the right side of the precordium in various types of heart disease.

METHODS AND MATERIAL

We are reporting here only those cases in which it was possible to obtain leads from the cavity of the right auricle and a lead from at least one point in the cavity of the right ventricle.

The fifteen patients studied have been divided into four groups. *Group A* contains six patients with pulmonary stenosis with or without the other features of the tetralogy of Fallot. These patients were cyanotic and all presented evidence of pronounced right ventricular enlargement. *Group B* consists of three patients with essential hypertension and varying degrees of left ventricular enlargement. *Group C* is made up of two hypertensive patients with right bundle branch block. The remaining patients, constituting *Group D*, did not display abnormal preponderance of either ventricle. One had a patent ductus arteriosus; one had had a pericardiectomy for constrictive pericarditis; and two were normal.

All intracavitary electrocardiograms were recorded simultaneously with Lead V₁ by means of a Sanborn Tri-beam Electrocardiograph. Most of the intra-auricular tracings were taken with this instrument operating at the standard sensitivity; in the majority of the intraventricular tracings a deflection of 1.0 cm. represents a potential difference of 3.0 millivolts.

In most instances the electrocardiographic observations were supplemented by measurements of the intracavitary pressures and of the oxygen content of the blood in the chambers on the right side of the heart. In the early cases the catheters used were of the type in which a small wire, terminating in an electrode, is embedded in the catheter wall. Catheters of this kind were found to have two disadvantages: the wire incorporated in the wall reduces the size of the lumen, which makes the withdrawal of blood samples difficult, and by decreasing the flexibility of the catheter, makes its introduction into the right ventricle and the pulmonary artery more difficult.

We, therefore, adopted the following technique. An ordinary 8F or 9F Cournand-type single lumen catheter was first advanced as far as desired. A wire stylet* of spring steel was then advanced through the catheter until its end was within two to three inches of the orifice. The wire was led out of the proximal end of the catheter through a hole bored near the outlet of a standard three-way stopcock, and connected to the electrocardiograph. Inasmuch as the stylet

*The stylets used were supplied by the United States Catheter and Instrument Co. for use with the Cournand catheter. They were of stainless steel, 0.016 inch in diameter, and the end was previously heated to form a small bead and thus prevent injury to the inner surface of the catheter during the insertion of the wire. Before each use the stylet was examined and tested carefully for possible flaws, to guard against the possibility of breakage during the process of insertion.

entered beyond the valve in the stopcock, it was possible to record pressures, to draw samples, or to maintain the infusion without altering the position of the recording wire within the catheter. When electrocardiographic tracings were taken, valuable information as to the location of the catheter tip could be obtained by recording the pressure at its orifice or by obtaining a sample of blood. The presence of the wire within the lumen of the catheter did not appear to alter significantly the pressure tracings taken with a Hamilton manometer, nor did it induce thrombus formation during the withdrawal of blood samples. As a precaution against the latter complication, a high, local concentration of heparin within the catheter was insured, not only by the addition of ten units of heparin per liter to the infusion fluid, but also by the preliminary injection of a stronger concentration of heparin solution just prior to the blood sampling.

Although the distal end of the stylet was never at the end of the catheter, and in a few instances could not be advanced to a point less than four or five inches from it, the potential variations recorded were clearly those taking place at the catheter orifice, for the catheter was a nonconductor. The effect of increasing the distance from the distal end of the stylet to the tip of the catheter was examined and it was found that as this distance became larger the resistance in the electrocardiographic circuit rapidly increased. As this resistance rose, the tracing recorded showed increasing distortion due to stray sixty-cycle current. The general outline of the electrocardiographic deflections was not altered in other respects, even in instances in which the distance from the distal end of the stylet to the catheter tip was increased to as much as three feet. At this distance, however, the voltage of these deflections was only about one-half as great as when the end of the stylet was only a few inches from the orifice of the catheter (Fig. 1).

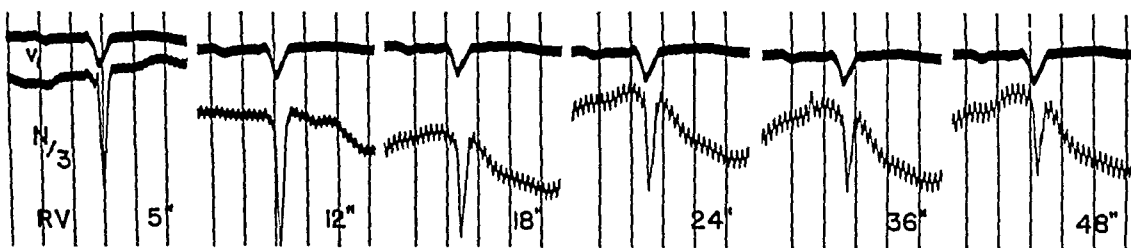


Fig. 1.—Normal subject. Upper beam, Lead V_1 . Lower beam, lead from the right ventricle taken with the electrocardiograph at normal sensitivity. The number at the right lower corner of each strip gives the distance in inches of the electrode tip from the intraventricular opening of the catheter.

The suitability, for our purpose, of wires made of various metals was examined by testing them in saline solutions. Although these tests showed that some metals gave larger polarization effects than others, there was no significant difference between the electrocardiograms obtained with different types of electrodes.*

*The authors are indebted to Professor Alfred L. Ferguson, Department of Chemistry, University of Michigan, for his valuable assistance in these problems.

Although the position of the catheter orifice could usually be ascertained by fluoroscopy, pressure readings were relied upon to determine without question that the catheter tip had entered or had been withdrawn from the right ventricle or pulmonary artery. An attempt was made to obtain records from at least three positions within the right ventricle. *Position I* is defined as that in which the catheter tip has just entered the right ventricle from the auricle and lies on the ventricular side of the tricuspid valve. The catheter orifice can be brought into this position by being advanced slowly until the smaller pressure variations characteristic of the right auricular cavity are replaced by the larger pressure variations characteristic of that of the right ventricle. *Position III* is that occupied by the catheter tip when it has been withdrawn from the pulmonary artery and lies on the ventricular side of the pulmonary valve. This position can be identified by the taking of a continuous pressure tracing as the catheter tip is being withdrawn after fluoroscopy has demonstrated its entrance into the pulmonary artery or one of its branches. The arrival of the catheter tip at the desired point is recognized by the sudden transition from the pulse pressures characteristic of the pulmonary artery to the larger pressure variations dependent upon the low diastolic pressures in the right ventricle. *Position II* is that occupied by the catheter tip when fluoroscopy shows that it lies near the cardiac apex and the pressure readings are those characteristic of the right ventricle. It was not always possible to obtain recordings from each of the three positions specified; for, in some instances, the catheter could not, for one reason or another, be advanced to the cardiac apex, or could not be introduced into the pulmonary artery.

In each case leads were taken from three positions in the right auricle. These were determined fluoroscopically and were called *high*, *mid*, and *low*. In the first of these, the catheter tip had just entered the right auricle from the superior vena cava; in the third, it was on the auricular side of the tricuspid valve; and in the second, it was approximately midway between the first and the third. Tracings were occasionally obtained from the superior vena cava and from points within the pulmonary artery. In addition, sometimes the catheter was advanced into the inferior vena cava and from there into branches of the hepatic vein, for the purpose of obtaining semidirect leads from the adjacent parts of the epicardial surface of the right or left ventricle (Fig. 5). Our experience with these last leads is limited, but it is felt that they may be of some value.

The intervals from the beginning of the QRS interval to the peak of the R wave and to the nadir of the S wave were measured* to the nearest thousandth of a second both in Lead V_1 and in leads from the cavity of the right ventricle. In some instances these measurements were extended to other leads or other deflections.

*All measurements were made by means of a device designed by Captain B. H. Eliot and manufactured by The Cambridge Company, Ossining, N. Y.

OBSERVATIONS

Extrasystoles.—Premature ectopic beats occurred frequently in some patients and infrequently or not at all in others. Auricular extrasystoles appeared while the catheter was in the right auricle in only one case (Fig. 2). Ventricular extrasystoles, however, were recorded on several occasions when the catheter was in Position II or III in the right ventricle, and could be made to disappear by withdrawing the catheter a few centimeters.

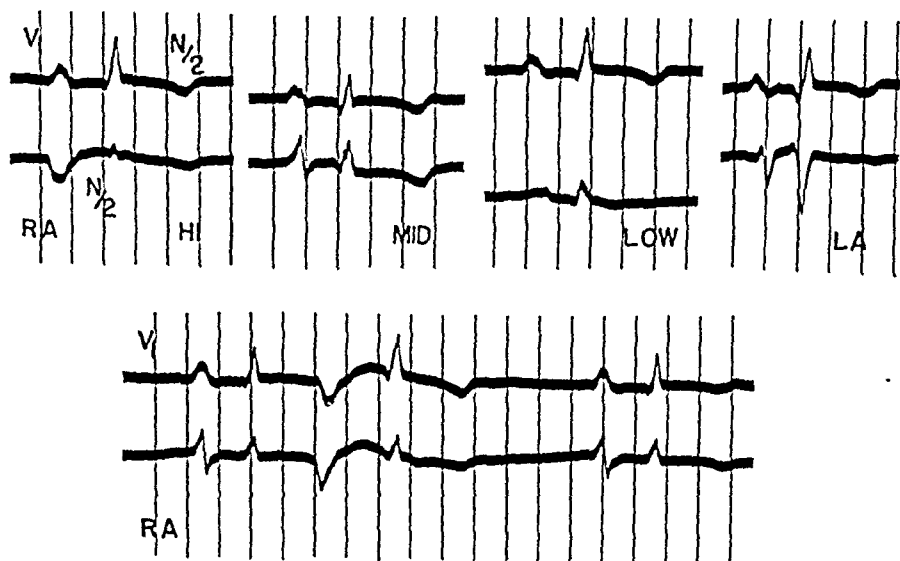


Fig. 2.—Tetralogy of Fallot. Upper beam, Lead V_1 taken with the electrocardiograph at one-half the normal ($N/2$) sensitivity. Lower beam, tracings from high (HI), mid-, and low positions in the right auricle, and from the left auricle (LA). The lower strip is a lead from the mid-position in the right auricle and the second complex represents an auricular extrasystole followed by a compensatory pause.

In the type of ventricular extrasystoles usually seen, Lead V_1 displayed a broad, bizarre QS complex (or a broad S wave preceded by a tiny R wave), and in the leads from within the right ventricle the normal initial positivity disappeared, so that the QRS complex was represented by a broad, downward deflection (Fig. 7). Such extrasystoles were attributed to a focus on the endocardial surface of the right ventricle. In one tracing, however, an ectopic ventricular beat occurring after a period of cardiac standstill induced by carotid sinus pressure is represented in Lead V_1 by a deep, broad S wave, preceded by a very small R wave, and in a lead from the cavity of the right ventricle (Position II), by a QRS complex consisting of a broad, notched R wave followed by a small S wave (Fig. 3). It is not certain that this ectopic beat was initiated by the presence of the catheter, but if it arose on the endocardial surface of the right ventricle, the electrocardiographic pattern which it produced is difficult to explain. In that case one would anticipate initial negativity of the ventricular cavity. It clearly had its origin near the cardiac base, for during the larger part of the QRS interval the excitation was spreading away from the precordial electrode near the base and toward the cavity electrode which was near the apex. There is a widespread belief that extrasystoles usually originate in the Purkinje system.⁷

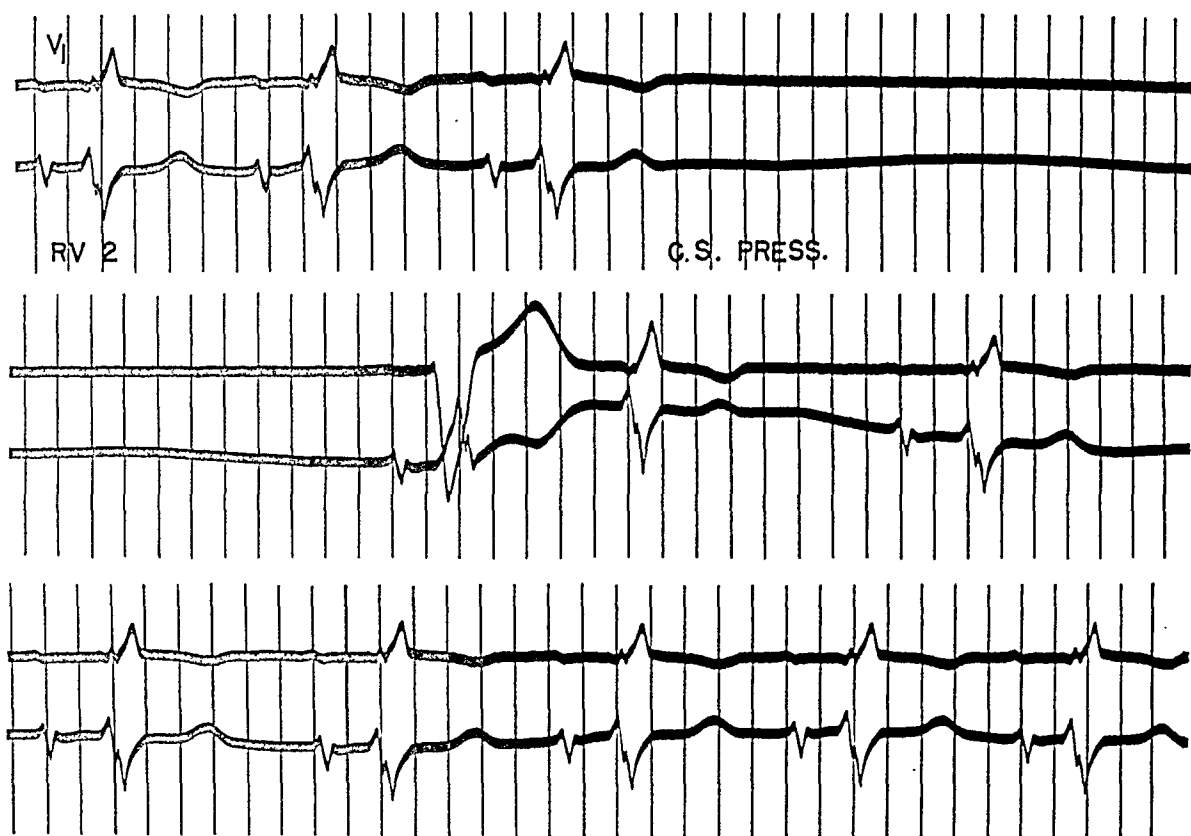


Fig. 3.—Right bundle branch block. Upper beam, Lead V_1 . Lower beam, lead from Position II in cavity of right ventricle taken at N/3 sensitivity. The three strips are continuous. Upper strip shows the beginning of prolonged pause following carotid sinus pressure. First complex in the second strip represents an ectopic beat (see text).

Endocardial Effects.—Upward displacement of the RS-T and P-R segments of variable magnitude occurred when the catheter came in contact with the endocardium of the right ventricle or right auricle (Fig. 5). The muscle region affected was obviously small, for displacement of the RS-T segment was never detected in the lead from the right side of the precordium (V_1). When the catheter was withdrawn one or two centimeters, the displacement in the cavity lead promptly disappeared and the first part of the QRS complex recorded from the new position generally resembled in form that recorded when the catheter was in contact with, or very close to the endocardium. In a few instances, however, it was noted that the peak of the initial R wave in the earlier tracing was considerably later (Fig. 8) than in that recorded after the catheter tip had been pulled back. This would seem to indicate that pressure of the catheter against the endocardium may in some instances delay conduction in the right Purkinje plexus, in one of the subdivisions of the right bundle branch, or in this structure itself. In one case of hypertension complete right bundle branch block was present only during the catheterization procedure.

Artifacts.—Occasionally, small, broad, positive waves (Fig. 4) occurred at regular intervals without relation to the heart beat. In a few instances these occurred sporadically. No explanation for these rhythmic deflections can be offered.

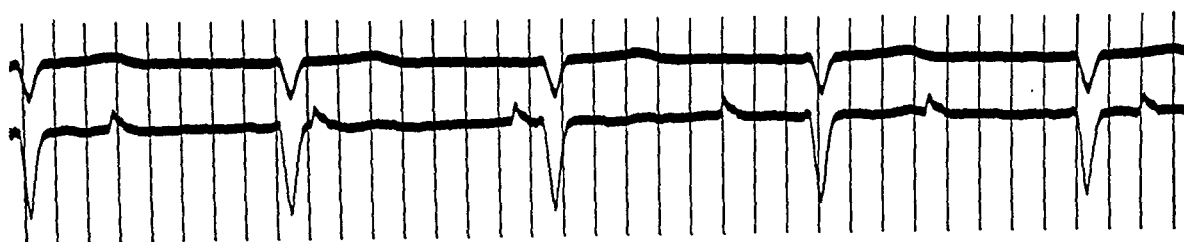


Fig. 4.—Case of hypertension. Rhythmic artifacts of unknown origin. Upper beam, Lead V_1 normal sensitivity. Lower beam, lead from Position II displaying broad, positive waves occurring fairly regularly but bearing no relation to the events of the cardiac cycle. P waves can be seen indistinctly in both upper and lower tracings and the P-R interval is constant.

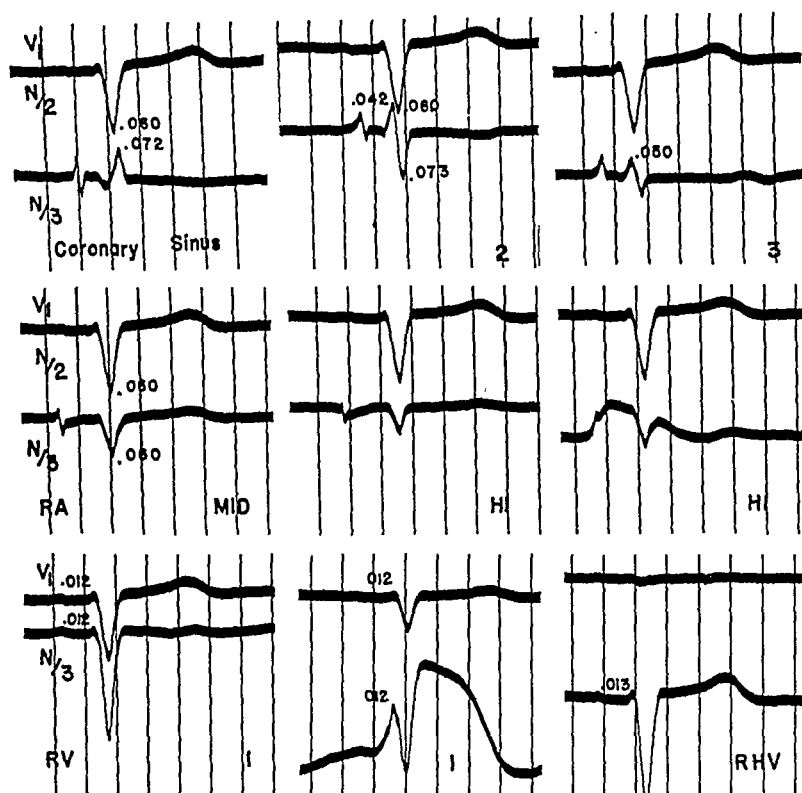


Fig. 5.—Essential hypertension. Upper beam, Lead V_1 taken at $N/2$ sensitivity. In the second strip of the third row the sensitivity of the upper beam is less than normal and in the third strip it has diminished to almost zero. The lower beam of the upper row shows leads from three different positions in the coronary sinus and in contrast to the leads from the auricular cavity exhibits a short P-R interval and larger R deflections. Lower beam of the second row, leads from the right auricle. The third strip in this row is from the same region as the second, but the electrode was against the auricular wall. In the third row the lower beam represents a lead from Position I in the right ventricle; first, with the catheter free in the cavity, and second, with the catheter in contact with the endocardium. The third and last strip is a lead from the right hepatic vein; the ventricular complex is like that of the intracavitary leads except that the T wave is upright.

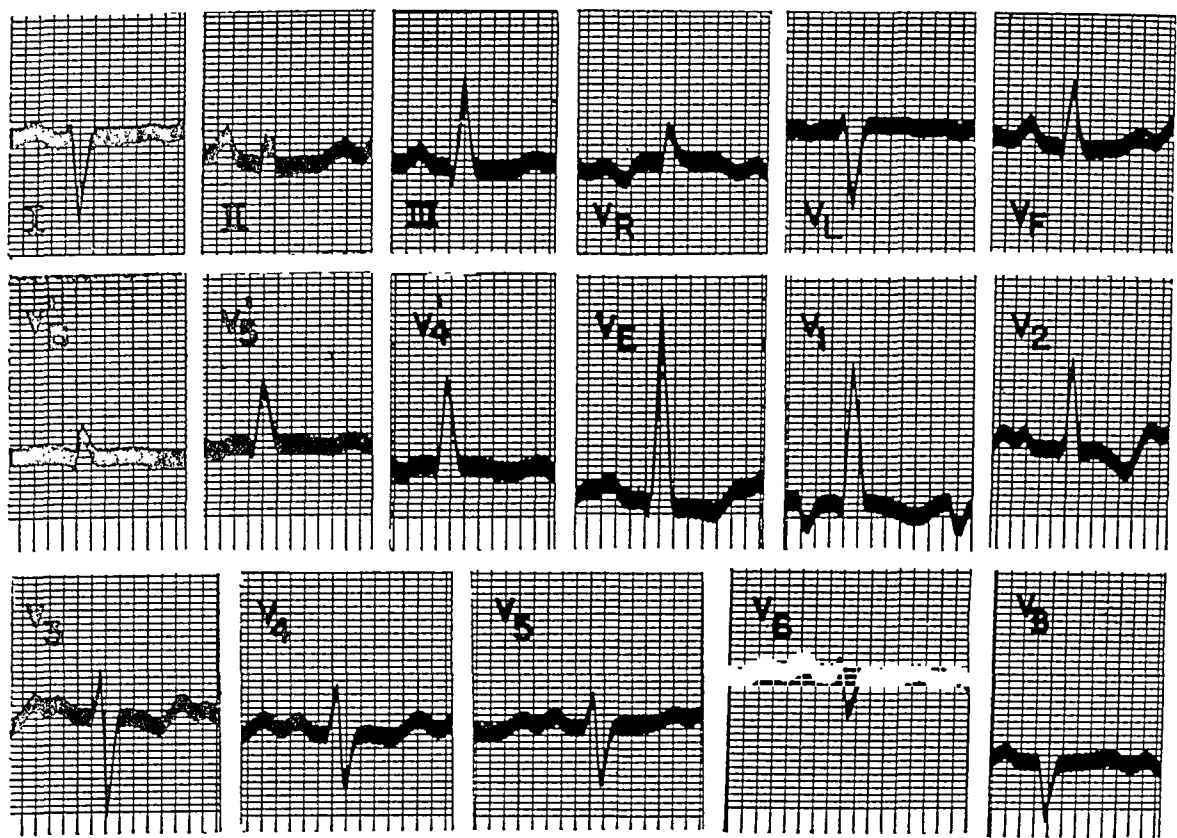


Fig. 6A. Tetralogy of Fallot. Standard and augmented unipolar limb leads. Second and third rows show six standard precordial leads; a lead from the ensiform process (V_E); a lead from the angle of the scapula at the level of the apex (V_B). The V_3 is a lead from a point on the right side of the chest corresponding to the point on the left side from which V_3 is taken. The symbols V_4 , V_5 , etc., have the same significance.

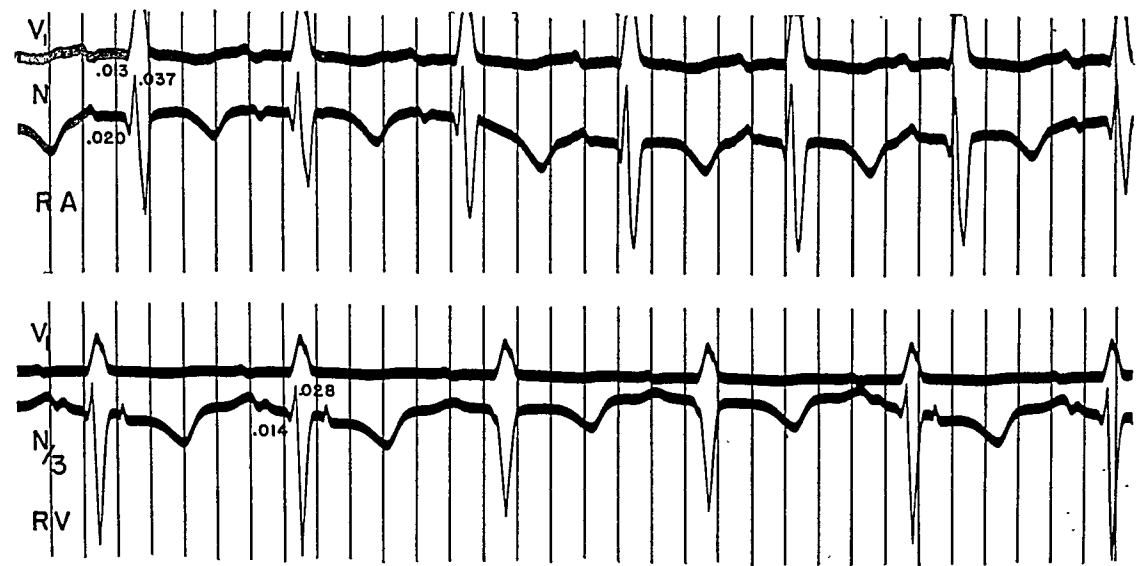


Fig. 6B.—Same patient as Fig. 6A.—Upper beam, Lead V_1 . In the upper row Lead V_1 is at normal sensitivity and the lower beam shows a lead from the right auricle taken at normal sensitivity. The variations in the form of the complexes are due to respiratory changes in the position of the electrode (see text). In the lower strip V_1 is at $N/2$ sensitivity and the lower beam shows a lead from within the right ventricle taken at $N/3$ sensitivity. Here also the variations in the form of the complexes are due to respiratory movements of the catheter tip.

Intra-auricular Electrocardiograms.—In general, our observations are in agreement with those of previous workers^{4,5,6} and are in accord with the predictions of the dipole theory.⁸ When the catheter tip is above the sinus node so that the auricular excitation wave spreads away from it, the P wave lies entirely below the isoelectric level. When the exploring electrode is in the middle of the auricular cavity so that the impulse first approaches, and then passes it, the P wave is of the RS type, with the peak of the R wave representing the arrival of the impulse at the level of the electrode. In leads from the lowest portion of the auricular cavity the P wave is predominantly positive (Fig. 7). In one instance it was observed that the auricular complex regularly passed through the three forms, that is, from positive to diphasic to negative, while the P-R interval remained constant (Fig. 6*B*). It was apparent that this cycle was due to respiratory variations in the position of the catheter tip. In a few instances we were able to produce similar changes in the P waves by instructing the pa-

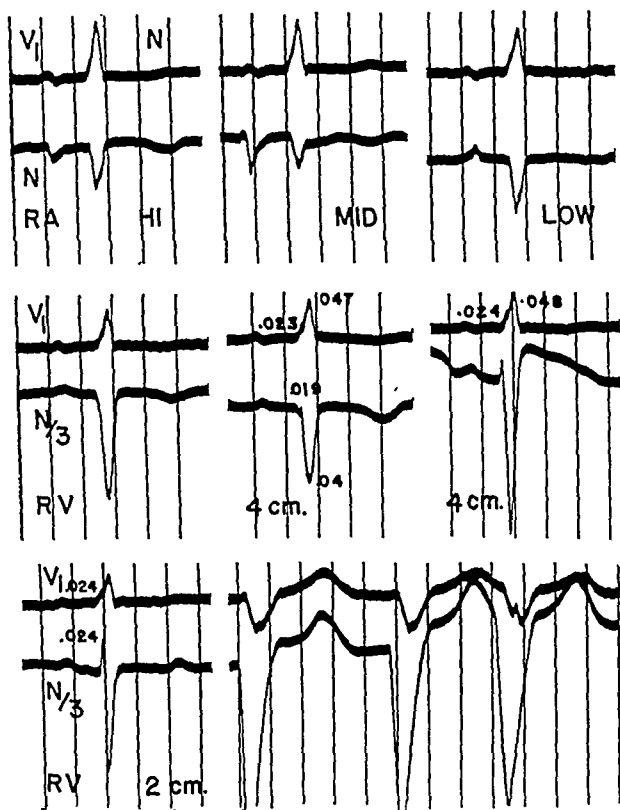


Fig. 7.—Tetralogy of Fallot. Upper beam, Lead V_1 . The electrocardiograph was adjusted to normal sensitivity, but because of the condition of the batteries the sensitivity gradually fell to approximately $N/2$. Lower beam, upper row; leads from the right auricle. First strip of second row shows a lead from Position I in the right ventricle. The next two strips show leads from the right ventricle; fluoroscopic control showed the catheter tip to be 4.0 cm. to the left of the midsternal line. The catheter was against the endocardial wall when the second strip was taken. Lower beam, third row, shows a lead from within the right ventricle with the catheter tip 2.0 cm. to the left of the midsternal line. The last three complexes represent extrasystoles with the catheter at the same position. Note the close correspondence between the R wave of the cavity lead and the notch in V_1 when the catheter was not against the wall. The small numbers to the third decimal place indicate the time in seconds of the adjacent peak with reference to the beginning of the QRS interval.

tients to breathe deeply. With the electrode in the midauricular position, the P waves were of the RS type during quiet respiration. During inspiration the electrode shifted to the upper portion of the auricle, and the P wave was of the QS type, whereas in expiration when the electrode moved into the lower portion of the auricular cavity, the P wave was upright.

In one case of congenital heart disease the P waves in the leads from the right side of the precordium were broad and notched. Because of the presence of a patent interauricular septal defect, it was possible in this instance to obtain electrocardiograms from the midportions of both the right and left auricles. In the lead from the right auricle the intrinsic deflection corresponded in time to the first notch of the P wave of Lead V₁. In the lead from the left auricle the P-R interval was shorter and the intrinsic deflection corresponded in time to the second notch of the P wave in the precordial lead. The QRS complex of the lead from the right auricle differed strikingly from that of the lead from the left. The former was dominated by a large R wave, whereas the chief deflection of the latter was downward (Fig. 2). The patient had extreme right ventricle enlargement and it is suggested that the lead from the right auricle reflected the late activation of the base of the hypertrophied right ventricle, and that from the left auricle, the negativity of the left ventricular cavity.

In another instance, fluoroscopy, blood sample showing an oxygen content of seven volumes per cent, and extremely low pressure readings indicated that the catheter was in the coronary sinus. The tracing from this region, that is, the groove between the left auricle and the left ventricle, displayed a shorter P-R interval than that from the right auricle. This observation may be regarded as additional evidence that the left auricle is activated later than the right. The patient had left ventricular enlargement. In contrast to the observations on the patient with right ventricular enlargement, previously described, the QRS complex of the lead from the right auricle consisted of a QS wave. In the leads from different positions in the coronary sinus, however, the QRS complex displayed a prominent R wave (Fig. 5). These positive waves differed in time from one position to another and it is suggested that they reflect the activation of different portions of the base of the left ventricle.

Previous workers^{4,5} have noted that the complexes of leads from the upper levels of the right auricle are often similar in form to those of Lead V_R. The majority of our cases showed a resemblance of this kind. There were a few instances, however, in which the form of the QRS complex in Lead V_R was like that of the leads from the lower portion of the right auricle. Sometimes the QRS complex of the leads from the auricle displayed a prominent Q wave which preceded in time the initial positive ventricular deflection of the leads from the right ventricle. We have no adequate explanation for this early auricular negativity, but it is necessary to consider that an electrode in the right auricle may reflect the potential variations produced by the left, as well as those produced by the right ventricle.

Intraventricular Electrocardiograms.—Other investigators^{4,5,6} have observed that as a rule the cavity of the right ventricle is positive at the beginning of the

QRS interval. This initial positivity has been attributed to early activation of the upper portion of the septum from left to right; in other words, to what may be considered physiologic incomplete right bundle branch block. An initial R wave was present in the leads from the cavity of the right ventricle in all of our cases. The amplitude of this early R wave varied, however, with the position of the catheter within the right ventricle. The R wave of the lead from Position I was frequently smaller than that of the leads from Positions II and III; and, in a few instances it was absent so that the QRS complex was represented by a QS deflection (Fig. 7). This deflection often displayed a notch or slur on the descending limb, corresponding in time to the R wave recorded in the lead from Position II or III in the same case. When these notches or slurs occurred, they were not constantly present, but came and went rhythmically. In one instance, with the catheter tip at Position I there were periodic transitions from an uncomplicated QS wave, to one notched on its descending limb, and from this form to a complex of the RS type. In this case (Fig. 6B) there was an intraventricular septal defect, and we considered the possibility that the catheter tip was entering and leaving the left ventricle. It may well be, however, that the variations in question were due to changes in the position of the exploring electrode in relation to the septum. As in the case of the similar variations in the auricular complex seen in auricular leads, we examined the effect of respiration upon the form of the complexes of intraventricular leads in several instances. It was found that during deep inspiration, which would be expected to shift the tip of the catheter toward the base of the heart, the initial R wave sometimes became smaller, whereas expiration made it larger (Fig. 9B). This finding is in accord with the observation that the R wave is ordinarily smaller in the lead from Position I than in that from Position II or III. It seems to us necessary to re-examine the concept that the uppermost part of the left side of the septum is activated earlier than any other.

The P waves of the intraventricular tracings were generally small and upright and the T waves were usually inverted. Exceptions to the latter rule will be discussed in a later section.

Relations Between Precordial Lead V_1 and Leads From the Right Ventricle.— Since V_1 is the precordial lead which is thought to reflect best the potential variations of the surface of the right ventricle, it was considered desirable to compare this lead with the leads from different points within the right ventricle. We hoped in this way to obtain a better understanding of the form of the ventricular complex in leads from the right side of the precordium, particularly in cases of right ventricular enlargement and right bundle branch block. Before presenting the findings in each of our four groups of patients, it seems appropriate to consider briefly a few of the concepts involved in a discussion of this type.

Let us consider, to begin with, the forces produced by activation of the septum in a direction perpendicular or nearly perpendicular to its endocardial faces. The potentials of the two ventricular cavities may be expected to differ in sign only when there are one or more boundaries between active and resting muscle in the septum. When one side of the septum is activated before the other, the

homolateral cavity is initially negative and the contralateral, initially positive. The normal, initial positivity of the right ventricular cavity in man is, therefore, attributed to early activation of the septum from left to right.

We may conclude, then, that activation of the septum in the normal fashion has opposite effects upon the potentials of the two cavities. It has the same effect upon each cavity and the epicardial surface of the free ventricular wall which bounds it. In contrast, the activation in the normal fashion of one of the free ventricular walls has opposite effects upon the potentials of its inner and outer surfaces, but affects the potentials of both ventricular cavities in the same way. These statements, of course, concern the sign of the potentials referred to, not their magnitude. When a boundary between active and resting muscle is established between the cavity and the epicardial surface of the right ventricle by an impulse spreading through its free anterior wall from within outward, the presence of this boundary will tend to make the epicardial surface of the wall positive and the ventricular cavity negative. The potential of the precordium is under all ordinary circumstances of the same sign with reference to an indifferent point, such as the central terminal, as that of the nearest part of the epicardial surface. But the magnitude of the potential of the precordium in comparison with that of the nearest part of the epicardium is dependent upon a variety of factors and is not easily predictable.

With reference to the comparison of the ventricular complexes of a lead from the right side of the precordium and the ventricular complexes of a lead from the cavity of the right ventricle, the following conclusions seem to be justifiable when, but only when, the ventricles are responding to impulses which reach them solely by way of the bundle of His, regardless of whether all subdivisions of this bundle are conducting normally. When a deflection in one direction occurs in the precordial lead simultaneously with a deflection in the opposite direction in the cavity lead, both deflections should be attributed to forces across a boundary between active and resting muscle in the free wall of the right ventricle. On the other hand, when a deflection in one direction in the precordial lead occurs simultaneously with a deflection in the same direction in the cavity lead, it is justifiable to conclude that the cavity deflection is shaped by forces arising at a boundary between active and resting muscle lying in the ventricular septum or the free wall of the left ventricle. The precordial deflection must be attributed in part to the same forces, but the possibility that it also represents forces generated in the free wall of the right ventricle cannot be excluded.

The initial activation of the septum from left to right which normally occurs prior to the activation of the free wall of the ventricles is represented by an R wave in the leads from the precordium which reflect the potential variations of the right side of the septum (Lead V_1 , and possibly Leads V_2 and V_E) and by a Q wave in those leads which reflect the potential variations of the left side of the septum (Leads V_5 and V_6 in about 50 per cent of normal subjects and leads from the left back).

In normal subjects and in patients with left ventricular enlargement, the small initial R deflection which occurs in the leads from the right side of the

precordium is more or less simultaneous with the initial R wave of the leads from the cavity of the right ventricle. It is justifiable, therefore, to conclude that the precordial R wave is due in part to forces of septal origin. After the inscription of this initial R wave the precordium and the cavity of the right ventricle are negative, and it is clear that this negativity is due to activation of the septum from right to left, to activation of the free walls of the two ventricles from within outward, or to both. The rapid increase in the negativity of the right ventricular cavity early in the QRS interval, for which these septal and left ventricular forces are responsible, causes the part of the precordial R wave due to activation of the thin free wall of the right ventricle to be much less conspicuous than it would be if it were written on a horizontal base line instead of a steep downward slope. The size of this R wave is not proportional to the voltage across the right ventricular wall. In right ventricular hypertrophy, on the other hand, the activation of the thick free wall of the right ventricle produces voltages that are greater or develop more rapidly than the septal and left ventricular forces in question and are also of longer duration. Under these circumstances the potential of the epicardium of the right ventricle and the right precordium are positive for a considerable period during which the potential of the ventricular cavity is negative. In right bundle branch block the activation of the free wall of the right ventricle occurs so late in the QRS interval that the forces which it produces are unopposed. Here again the potential of the cavity and the potential of the epicardial surface of the right ventricle are opposite in sign.

The principles applicable to interpretation of the deflections produced by depolarization are equally valid in the interpretation of those which accompany repolarization. The T wave in leads from the epicardial side of the free wall of the right ventricle will differ in direction from that inscribed in leads from the ventricular cavity side only when the forces produced by repolarization of the free wall of the right ventricle are not overbalanced by those produced by repolarization of other parts of the heart. In the majority of normal adults the T waves are upright in the leads from the right side of the precordium and inverted in leads from the right ventricular cavity. This implies that repolarization takes place earlier on the epicardial than on the endocardial side of the right ventricular wall; in other words, the repolarization process spreads from the epicardial toward the endocardial surface. When the T waves have the same direction in leads from both sides of the free wall of the right ventricle, their form is evidently determined to a large extent by forces produced by repolarization of the septum or the free wall of the left ventricle. Under these circumstances the present method of investigation does not furnish reliable information concerning the direction of repolarization in the free wall of the right ventricle. Such information could be obtained only by measuring the voltage across the wall during the inscription of the T wave by leading from its endocardial to its epicardial surface.

Group. 1. Cases of Right Ventricular Enlargement.—The majority of our cases of this kind were examples of extreme right ventricular enlargement. The precordial electrocardiogram, therefore, was of the type displaying tall R

waves in the leads from the right side of the precordium and small R and deep S waves in the leads from the left side (Fig. 6A). In one case in which the clinical diagnosis was tetralogy of Fallot the large R deflection of the leads from the right side of the precordium was preceded by a Q wave (Fig. 6A). The leads from within the right ventricle also displayed a Q deflection and this was simultaneous with the Q wave in lead V₁ (Fig. 6B). It can hardly be doubted that the precordial Q wave and the cavity Q wave are alike in origin, but there is no entirely satisfactory explanation for the occurrence of a Q deflection in leads from the right ventricular cavity. Several possibilities may be considered. There was no Q wave in the leads from the left side of the precordium and the left side of the back, but this deflection occurred in all the leads from the right side of the precordium and in a lead from the posterior aspect of the right chest (Fig. 6A). If the R wave of the cavity lead in this case is attributed to activation of the left side of the septum before the excitation process reached the right side by way of the right branch of the bundle of His, the still earlier Q deflection must be ascribed to an excitatory process traveling away from the exploring electrode through left ventricular muscle. If the cavity Q wave were due to forces arising in the free wall of the right ventricle, it would be expected to be simultaneous with an upward deflection in Lead V₁. If we ascribe this deflection to activation of the septum from right to left, we must assume that the right side of the septum was activated before the left; or, that the two sides of the septum were activated simultaneously and the forces produced by activation of the right side of this structure overbalanced those produced by activation of its left side during the earliest phases of the QRS interval. It seems unlikely that there is a minor defect in left bundle branch conduction in those cases of right ventricular hypertrophy in which the right ventricular cavity is initially negative, for this hypothesis does not satisfactorily account for the rather prominent R wave which follows the small Q wave in right cavity leads. It is conceivable that in these cases excitation begins or develops most rapidly in the free wall of the left ventricle or in one of the papillary muscles in the left or right side of the septum. Whether the presence of a defect in the ventricular septum is in any way responsible for the phenomenon in question is also a matter for conjecture. It is hardly worth while to speculate further until more data are available, but it should be noted that occasionally in dogs there is initial negativity of the right ventricular cavity, even in the presence of right bundle branch block.^{2, Fig. 6}

Four of our patients with right ventricular enlargement displayed notching or slurring of the upstroke of the tall R wave of Lead V₁. In three of these the R-wave peak in the cavity lead corresponded closely in time to the notch or slur in Lead V₁ and the peak of the R wave in the precordial lead was related closely in time to the S deflection of the leads from the cavity of the right ventricle (Fig. 7). It seems evident, therefore, that in cases of this type the R wave in Lead V₁ represents forces produced by activation of the septum from left to right followed closely by the activation of the free wall of the right ventricle from within outward. The form of the precordial QRS complex in these cases is reminiscent of that seen in cases of complete right bundle branch block. In these the QRS interval is longer (0.12 second or more), but the R wave of

Lead V_1 is often conspicuously slurred and notched. Leads from points farther to the right, however, usually display double R waves. In the cases with which we are dealing, the QRS interval measured less than 0.10 second, but because of the form of the QRS complex in Lead V_1 , incomplete right bundle branch block was frequently suspected. The initial R deflection in the leads from the right ventricular cavity in our four cases, however, does not differ appreciably from that recorded in normal subjects. Furthermore, leads from points to the right of the right sternal margin did not display double R waves. Thus, it seems unlikely that more than the physiologic degree of incomplete right bundle branch block was present in these cases.

In five of the six cases of Group 1, Lead V_R displayed a late R wave and the QRS complex of this lead resembled that of one or more of the leads from the cavity of the right auricle.

In three cases the T waves were upright in the leads from the right side of the precordium and inverted in those from the right ventricular cavity. This pattern is the rule in normal subjects and, as already noted, suggests that repolarization takes place earlier on the epicardial side than on the endocardial side of the right ventricular wall. In the other three cases the T waves were inverted both in the leads from the right side of the precordium and in those from the right ventricle, and this T-wave pattern is ascribed to the course of repolarization in parts of the heart other than the free wall of the right ventricle. It does not permit any conclusion as to whether repolarization of this wall begins on its inner or outer surface. It should be noted, however, that in all six cases of right ventricular enlargement the QRST area of the cavity leads was clearly negative, whereas that of Lead V_1 was clearly positive. This indicates that the gradient in the length of systole, or speaking more strictly, in the time course of excitation and recovery, across the free wall of the right ventricle was of the same kind in all of them.

Group 2. Right Bundle Branch Block.—The two patients in this group had moderate hypertension. One patient displayed complete right bundle branch block only during catheterization, and it is possible that the conduction defect was initiated by this procedure. The other patient was unusual in that the right bundle branch block usually disappeared when the heart rate was reduced by carotid sinus pressure. During the catheterization carotid sinus pressure caused pronounced cardiac slowing but did not abolish the block (Fig. 3).

In both cases there was a broad, initial R wave in the leads from the right ventricle. As in the other cases the size of this deflection varied with the level of the electrode, and in both instances its voltage was smaller in the lead from Position I than in the lead from Position II. In each case it was clear that the initial positivity of the cavity was responsible, at least in part, for the early R wave in Lead V_1 , whereas the S wave of the intraventricular lead corresponded in time to the late R' of the precordial tracing. In one case the precordial R wave was distinctly bifid and the late R' had a notch on its descending limb (Fig. 8). This notch corresponded in time to the nadir of the S wave of the intraventricular lead, and this part of R' is clearly attributable to the activation of the

free wall of the right ventricle. The depression which separates the R and R' deflections in Lead V₁ corresponds in time to the notch on the intraventricular R wave and it seems likely that both represent the effect of forces produced by activation of the free wall of the left ventricle. Thus, in those cases of complete right bundle branch block in which the secondary R' wave in Lead V₁ is broad, and particularly when it is notched, the first part of this deflection is evidently due mainly to activation of the septum from left to right, whereas its final part represents activation of the free wall of the right ventricle. In cases of right bundle branch block in which the R' deflection of Lead V₁ is slender and unnotched, it is still uncertain whether it is due solely to activation of the free wall of the right ventricle, or contains septal components also.

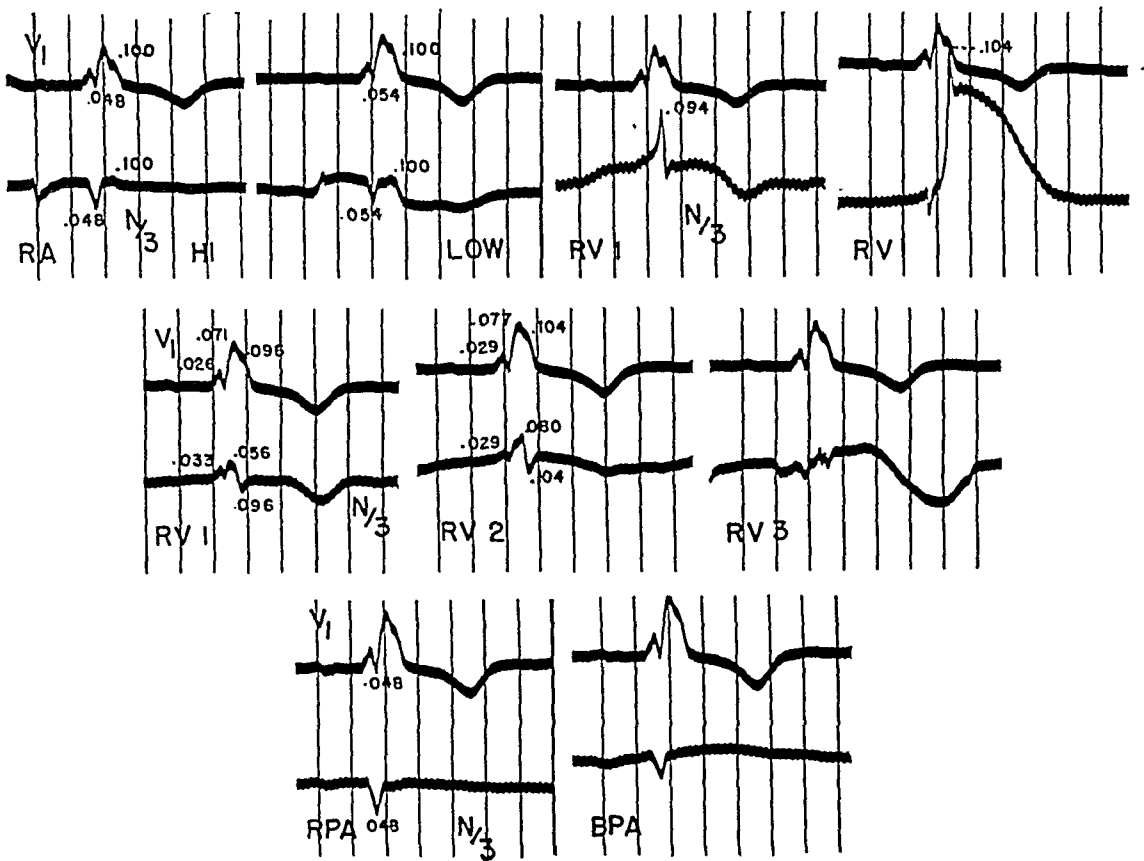


Fig. 8.—Right bundle branch block. Upper beam, Lead V₁. Upper row, the first two strips show leads from the right auricle. The last two strips show a lead from Position I in the right ventricle, with the catheter tip first about 1.0 cm. from the endocardium and then in contact with it. The second row shows leads from three positions in the right ventricle. The tracing from Position III shows numerous artifacts. The two strips of the third row show leads from the right pulmonary artery (RPA) and the bifurcation of the pulmonary artery (BPA). The small numbers record in seconds the time of the adjacent peaks in relation to the beginning of the QRS complex in Lead V₁ or in the cavity lead.

One of our records shows a QRS complex of the normal type, indicating that the bundle branch block temporarily disappeared. In Lead V₁ this complex is of RS form and measures 0.08 second in duration. In the lead from the right ventricle the same beat is represented by a QS complex or a downward deflection preceded by a tiny R wave. The intracavitary R wave measured 0.04

second in duration in one and 0.09 second in the other case of right bundle branch block. In our other cases the duration of this deflection averaged about 0.02 second, the minimum being 0.010 second and the maximum, 0.035 second (the latter occurring in the tracing of a normal subject). The height of this R wave deflection in the two cases of right bundle branch block was no greater than its height in our other cases, and it seems unlikely that its voltage can be depended upon to differentiate between right bundle branch block and normal intraventricular conduction. On the other hand, its duration may be helpful in making this differentiation.

In our two cases of right bundle branch block the intra-auricular leads displayed a broad, late R wave similar to that present in Lead V_R .

Group 3. Left Ventricular Enlargement.—There were three patients in this group, all with prominent left ventricular enlargement. In all of them the leads from the right ventricle displayed a small initial R wave (Figs. 5 and 9B). The duration of this deflection was approximately the same as in the cases of right ventricular enlargement, but on the whole its amplitude was smaller. If its small size were due to less early activation of the left side of the septum, one would expect the Q waves of the leads from the left side of the precordium to be correspondingly reduced in size. In the few patients whom we were able to examine, this was not the case. There are cases of left ventricular enlargement in which the initial R wave of the leads from the right side of the precordium is minute or entirely absent and intracavitary leads would be of great interest in such cases. No cases of this kind are included in our series.

In two cases there was a late R wave in the leads from the lower portion of the right auricle (Fig. 9B). It is suggested that this deflection was due to activation of the base of the left ventricle. In one of these Lead V_R displayed a similar deflection (Fig. 9A). In the remaining two cases the QRS complex of Lead V_R consisted of a QS complex.

The T waves were inverted in the intraventricular leads in one case and low but upright in the other two. The T waves were upright in the leads from the right side of the precordium but inverted in all those from the left side in all three cases.

Group 4.—The remaining four patients form a heterogeneous group, but in none was cardiac enlargement present. The intracavitary R waves corresponded closely in time with the R waves of Lead V_1 . In all instances but one the initial R wave of the right ventricular cavity measured less than 0.024 second in duration and was not conspicuously tall. The exceptional patient was a young man of twenty without apparent heart disease whose tracings in the leads from the right ventricle displayed R waves which were unusually broad (0.035 second) and tall compared with the S wave (Fig. 10B). This patient's precordial electrocardiogram showed a QRS interval of 0.09 second, tall R waves in the leads from the right side of the precordium, especially Lead V_E , and Q waves in Leads V_5 and V_6 (Fig. 10A). In Lead V'_4 (a lead from the right side of the chest corresponding to Lead V_4) the sole QRS deflection was upward. We have

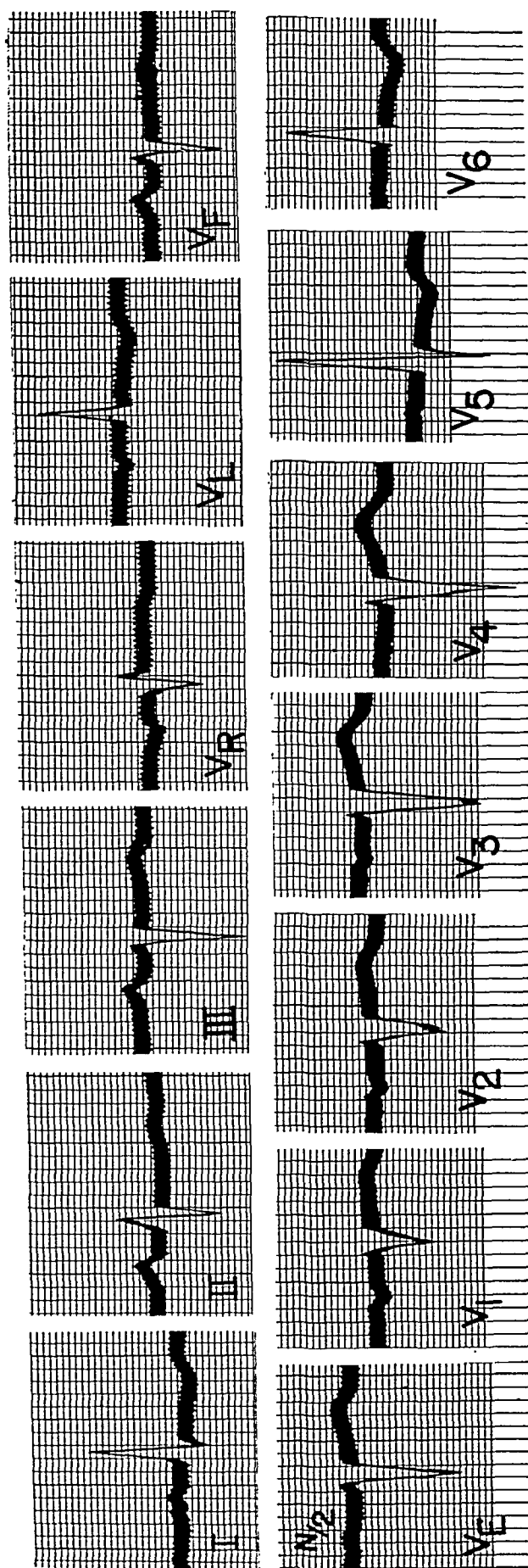


Fig. 9A.—Essential hypertension. Upper row, the standard and augmented unipolar leads. Lower row, precordial electrocardiograms recorded at N/2 sensitivity.

wondered whether an abnormal delay in the activation of the right ventricle was present in this case. Certainly, if intracavitary leads and leads from the right side of the chest had not been taken, no abnormality would have been suspected. It is our opinion that in some normal subjects the normal difference in the time of activation of the two ventricles is greater than it is in others.

SUMMARY AND CONCLUSIONS

Intracavitary electrocardiography is useful for the purpose of ascertaining the effects of activation of the free wall of the right ventricle upon the form of the QRS complex of Lead V_1 in cases of right ventricular enlargement and right bundle branch block. The order in which the inner and outer layers of this wall are repolarized is disclosed by this method only when the T waves of the leads from the ventricular cavity and those of the leads from the right side of the precordium are opposite in direction.

1. In right ventricular enlargement the large R wave in Lead V_1 represents the activation of the free wall of the right ventricle. Notches or slurs on the upstroke of this deflection are apparently due to the activation of the septum

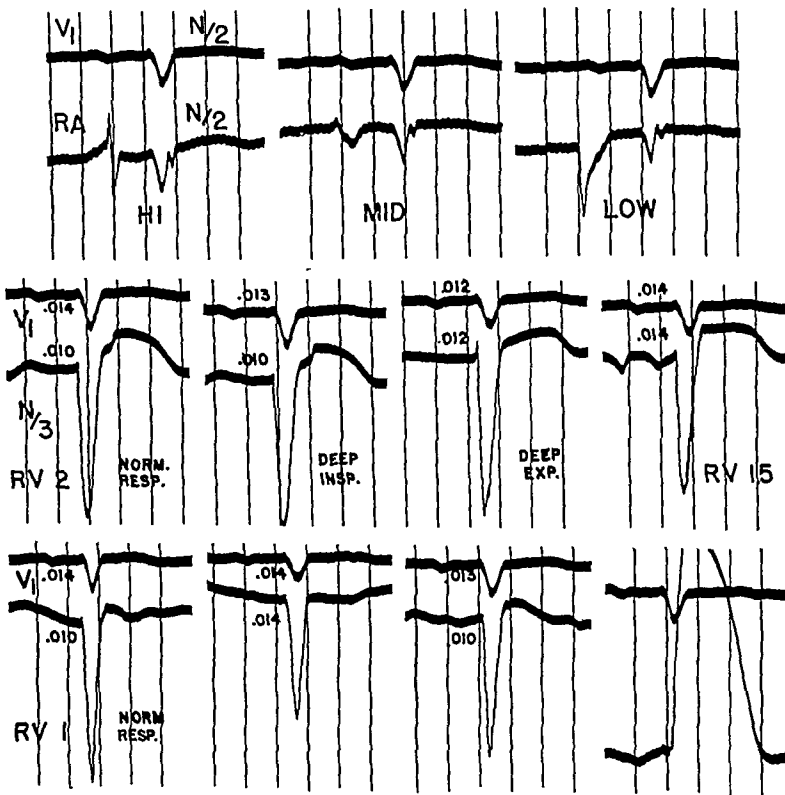


Fig. 9B.—Same patient as Fig. 9A. Upper beam, Lead V_1 . First row, leads from the right auricle. Second row, the first three tracings show a lead from Position II in the right ventricle during normal respiration, deep inspiration, and expiration, respectively. Last tracing of the second row is from position in the right ventricle midway between Positions I and II. Lower row, leads from Position I in the right ventricle during normal respiration, deep inspiration, and expiration, respectively. Last tracing taken when catheter tip was against endocardium at Position I.

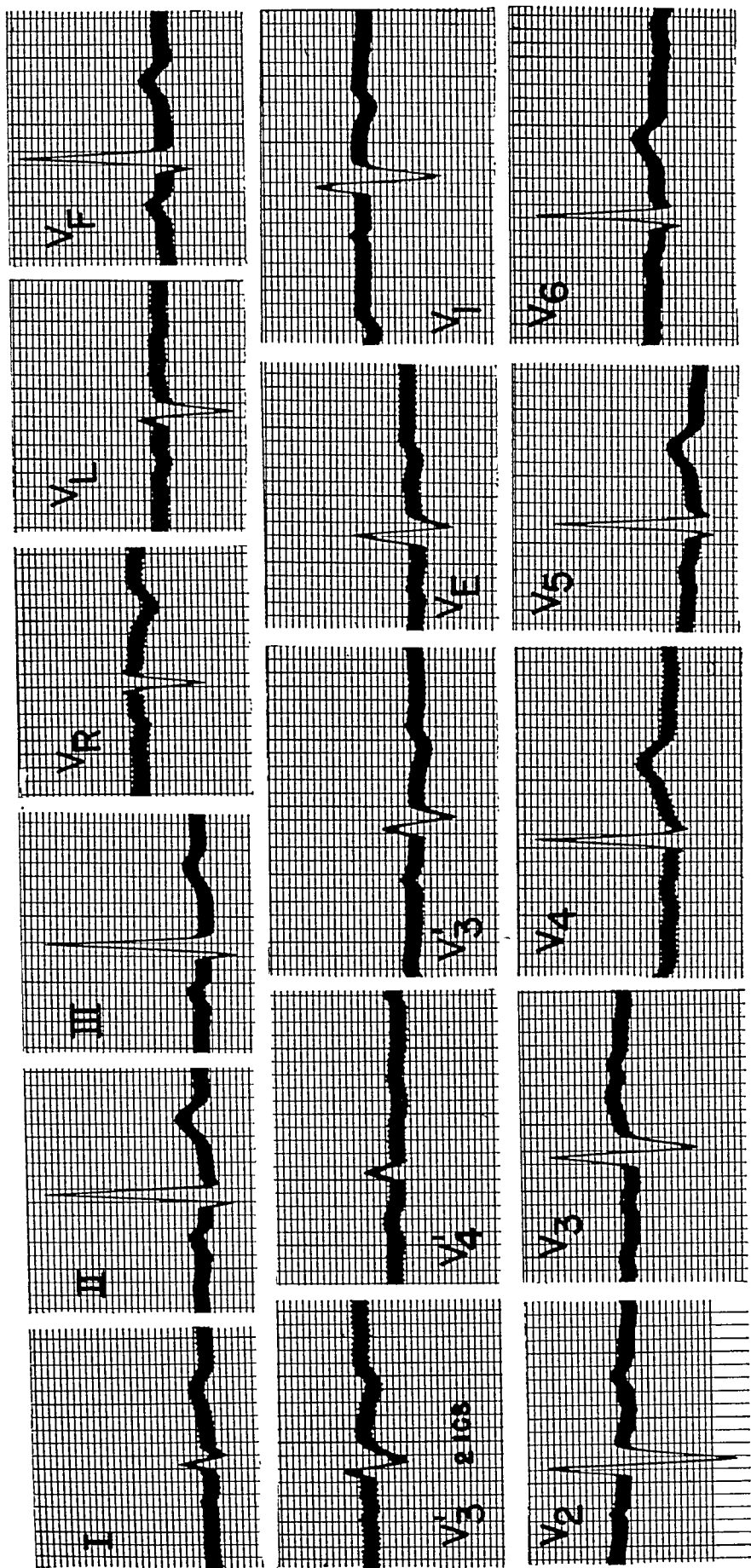


Fig. 10A.—Normal subject. Upper row, standard and augmented unipolar limb leads. Lower rows, leads from the chest. Symbols have the same significance as in previous figures. Lead V₃ was taken at the usual position and also at the second intercostal space.

from left to right and do not justify the conclusion that the right ventricle is activated abnormally late. In some cases of right ventricular enlargement in which there is a Q deflection in Lead V_1 , there is a simultaneous Q deflection in leads from the cavity of the right ventricle. The origin of this Q wave is obscure.

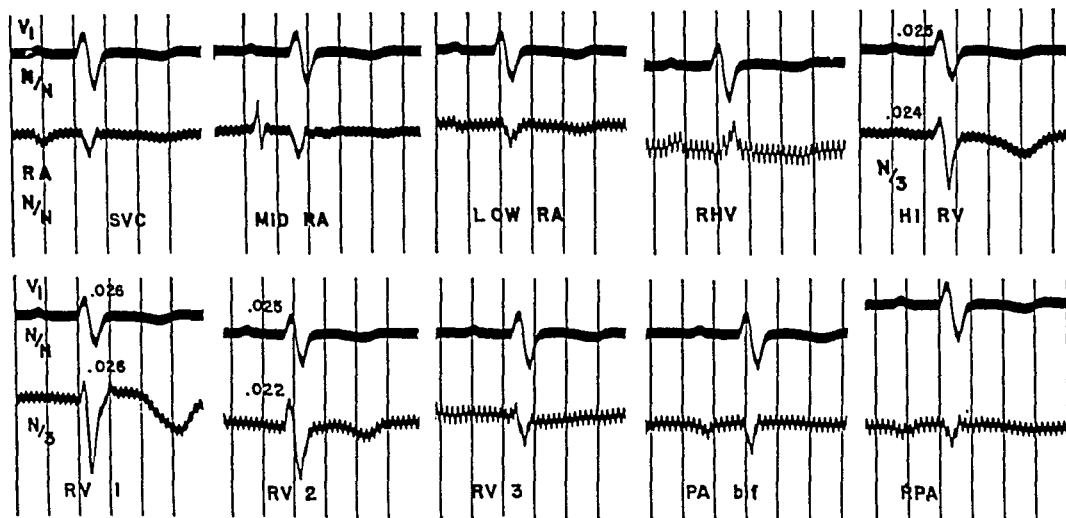


Fig. 10B.—From the same patient as Fig. 10A. Upper beam, Lead V_1 . Lower beam, leads from superior vena cava (SVC), mid-position in the right auricle (*mid RA*), lower position in the right auricle (*low RA*), and right hepatic vein (*RHV*). *Hi RV* is the same as Position I in the right ventricle (*RV1*), but the latter is from a point closer to the endocardium. *RV2* and *RV3* equal Positions II and III in the right ventricle. Last two strips show leads from the bifurcation of the pulmonary artery (*PA bif*) and from the right main branch of the pulmonary artery. Unfortunately, 60 cycle current was superimposed on several of the tracings.

2. In right bundle branch block the initial R wave in Lead V_1 is due to the activation of the septum from left to right. In those electrocardiograms in which the secondary R wave in Lead V_1 is broad and notched, the initial portion of this secondary R wave is due to the activation of the septum, and its final portion, to activation of the free wall of the right ventricle.

The height of the intracavitary R wave is not a useful criterion for the purpose of diagnosing conduction defects in the right branch of the bundle of His, but its duration may prove to be of greater value.

3. In normal subjects and in patients with left ventricular enlargement, the early activation of the septum from left to right contributes to the R wave of Lead V_1 and is responsible for the Q wave that occurs in Leads V_5 and V_6 .

4. Leads from the cavity of the right auricle and Lead V_R usually reflect the late activation of the base of the right ventricle when it is hypertrophied, and may in other instances reflect the late activation of the base of an hypertrophied left ventricle.

5. In some normal individuals the difference in the time of activation of the two ventricles is greater than in others. This greatly complicates the diagnosis of incomplete right bundle branch block.

6. In the free wall of the right ventricle the repolarization process ordinarily advances from the epicardial toward the endocardial surface.

The authors are greatly indebted to Dr. Frank N. Wilson for his many valuable suggestions and for his help in the preparation of this paper.

REFERENCES

1. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The Interpretation of the Galvanometric Curves Obtained When One Electrode is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface, *AM. HEART J.* 10:196, 1934.
2. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliviera, R., Scarsi, R., and Barker, P. S.: The Pre-cordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
3. Forssmann, W. I.: Die Sondierung des rechten Herzens, *Klin. Wchnschr.* 8:2085, 1929.
4. Hecht, H.: Potential Variations of the Right Auricular and Ventricular Cavities in Man, *AM. HEART J.* 32:39, 1946.
5. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiogram Obtained by Heart Catheterization in the Man, *AM. HEART J.* 33:604, 1947.
6. Sodi-Pallares, D., Vizcaino, M., Soberon, J., and Cabrera, E.: Comparative Study of the Intracavity Potential in Man and in Dog, *AM. HEART J.* 33:819, 1947.
7. Marcu, I.: Experimental Extrasystoles Elicited Through Artificial Stimulation of the Endocardium of the Dog, *AM. HEART J.* 12:301, 1936.
8. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Tissues Immersed in Extensive Conducting Media, *J. Gen. Physiol.* 16:423, 1933.

DURATION OF THE Q-T INTERVAL IN NORMAL PREGNANT WOMEN

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MEASUREMENT of the Q-T interval in the electrocardiogram has long been regarded as almost useless for any clinical purpose. It is known to be shortened by digitalis¹ and salicylates² and lengthened by hypocalcemia, quinidine, acute myocardial infarction, and congestive heart failure.^{3,4} However, since Taran and Szilagyi⁵ showed that the Q-T interval is abnormally prolonged in all cases of rheumatic carditis which they observed and that it is not prolonged in inactive rheumatic disease or in normal subjects, it has become a measurement of considerable significance in the evaluation of rheumatic carditis.

Various studies have been made to determine the normal limits of the Q-T interval in normal healthy individuals. These studies have been used as a base line to determine abnormal prolongation. Inasmuch as it is very important to make an early and correct diagnosis of active rheumatic carditis in pregnant women and in order to use the Q-T interval as one of the criteria for activity, it is first necessary to determine the normal range in healthy pregnant women. It seemed possible that the altered circulatory dynamics during pregnancy might have some effect on its duration.

METHOD

Electrocardiograms were taken on fifty normal women from the prenatal clinic. These covered the entire period of gestation. The electrocardiograms, consisting of the three standard limb leads and CF₄, were made with the subjects in the supine position. The instrument used was a Cambridge mobile electric model, with an independent Telechron timer. All measurements were made with the aid of a magnifying lens in all leads in which a clear curve was obtained. The cycle length (R-R) and the Q-T interval were determined from averages of all leads. Taran's modification of Bazett's formula* $\left(Q-T_c = \frac{Q-T}{\sqrt{R-R}} \right)$ was used.^{5,6}

This modification instead of using a constant K (=0.40) to determine the average normal Q-T at any given rate calculates a corrected Q-T† from any given measured Q-T interval and R-R. This provides an easy method of comparing any determination with a normal standard.

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* $Q-T = K \sqrt{R-R}$.

†Corrected to a cycle length of 1.00 second.

RESULTS

The results of these measurements and calculations are shown in Table I. Q-Tc ranged from 0.371 to 0.421, with an average value of 0.394. These figures are all below the commonly accepted upper limit of normal of 0.425 for adult women. The measured Q-T intervals were plotted against the R-R intervals on a scatter graph (Fig. 1) on which is shown Ashman and Hull's⁷ upper limit of normal and average normal, and Bazett's⁶ average normal for adult women. It is seen that all the measurements fall below the upper limit of normal and that they follow closely the curves for average normal. Breaking the figures down into the three trimesters of pregnancy gives average Q-Tc values of 0.390, 0.396, and 0.394 for the first, second, and third trimesters, respectively.

TABLE I. DURATION OF PREGNANCY, AGE SPREAD, AND MEASURED AND CORRECTED Q-T INTERVALS IN FIFTY PREGNANT WOMEN

CASE	DURATION OF PREGNANCY (MO.)	AGE (YEARS)	R-R (SEC.)	Q-T (SEC.)	Q-Tc (SEC.)	CASE	DURATION OF PREGNANCY (MO.)	AGE (YEARS)	R-R (SEC.)	Q-T (SEC.)	Q-Tc (SEC.)
1	9	19	0.620	0.325	0.414	26	6	23	0.706	0.329	0.391
2	8½	20	0.740	0.335	0.389	27	4	29	0.619	0.311	0.398
3	8½	20	0.735	0.340	0.397	28	2	23	0.850	0.361	0.392
4	6½	39	0.564	0.291	0.390	29	8	21	0.721	0.323	0.381
5	8	19	0.600	0.298	0.386	30	3	31	0.770	0.333	0.379
6	7½	23	0.762	0.338	0.387	31	3	29	0.763	0.337	0.385
7	2	29	0.660	0.321	0.395	32	5	27	0.705	0.325	0.387
8	6	25	0.658	0.323	0.400	33	3	21	0.680	0.330	0.399
9	9½	21	0.655	0.319	0.396	34	9	20	0.635	0.319	0.400
10	3	25	0.480	0.270	0.391	35	5½	31	0.750	0.350	0.405
11	7½	20	0.555	0.315	0.421	36	3	22	0.819	0.360	0.399
12	7	23	0.666	0.311	0.382	37	6½	26	0.570	0.295	0.392
13	4½	25	0.776	0.352	0.399	38	5½	26	0.710	0.349	0.415
14	6	27	0.600	0.320	0.413	39	6	38	0.626	0.331	0.416
15	3½	20	0.704	0.311	0.371	40	9	23	0.854	0.351	0.383
16	4	31	0.749	0.345	0.398	41	5	26	0.521	0.280	0.389
17	8½	32	0.521	0.280	0.389	42	4	21	0.715	0.327	0.387
18	7½	35	0.711	0.339	0.402	43	8	24	0.634	0.302	0.390
19	8½	24	0.570	0.290	0.383	44	8½	23	0.509	0.283	0.397
20	4	25	0.739	0.325	0.379	45	8½	24	0.666	0.318	0.391
21	2½	22	0.760	0.355	0.407	46	7	30	0.615	0.310	0.395
22	6	27	0.650	0.306	0.381	47	8	29	0.635	0.309	0.389
23	3½	24	0.611	0.303	0.389	48	9	20	0.520	0.287	0.397
24	6	24	0.522	0.292	0.403	49	3½	21	0.795	0.340	0.383
25	3	26	0.735	0.320	0.384	50	5	20	0.673	0.320	0.392
Average									0.656	0.320	0.394

COMMENT

Despite alterations in the circulatory dynamics during pregnancy, there is no significant variation in the duration of electrical systole from the average normal. This knowledge enables one to make use of the Q-T interval in determining the presence and the duration of active rheumatic carditis. Abnormally

prolonged Q-T intervals were found throughout the entire period of activity in three pregnant women admitted to Beth Israel Hospital with acute rheumatic carditis during the past year. Electrocardiograms before and after activity had normal Q-T intervals.

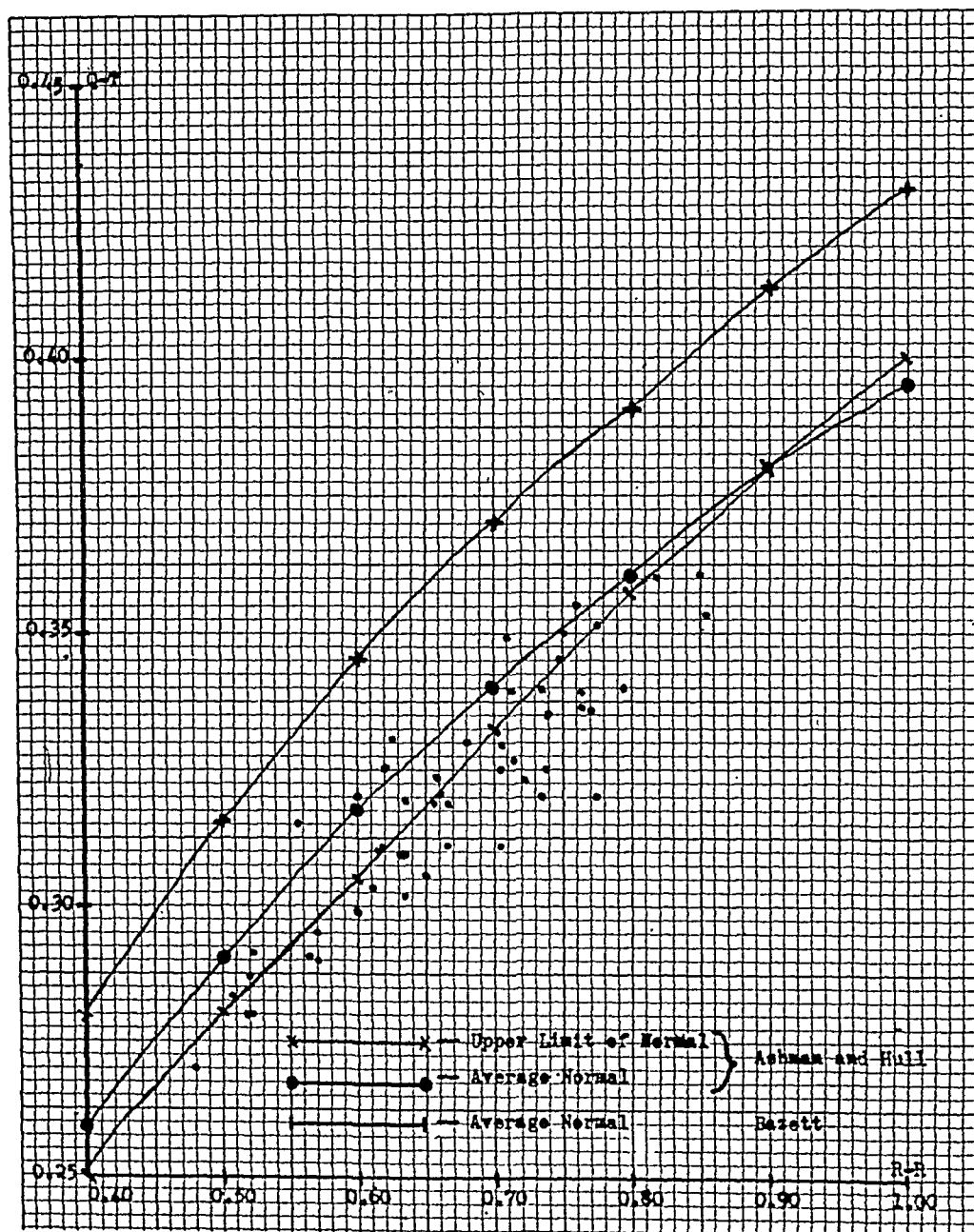


Fig. 1.—Measured Q-T intervals plotted against cycle length in seconds, and normal curves for adult women.

CONCLUSIONS

1. Measurements of the Q-T interval were done on the electrocardiograms of fifty pregnant women.
2. All measurements were found to fall within the normal limits as determined by previous studies done on normal adult women.
3. Making use of Q-Tc (the corrected Q-T interval),⁵ furnishes a simple means of determining whether a given measurement is above or below the normal range.
4. All corrected Q-T intervals in this series were below the commonly accepted upper limit of 0.425.

REFERENCES

1. Cheer, S. N., and Dieuaide, F. R.: Studies on Electrical Systole ("Q-T" Interval) of the Heart; Its Duration in Cardiac Failure, *J. Clin. Investigation* **10**:889, 1931.
2. Taran, L. M.: Personal communication.
3. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, ed. 4, New York, 1941, Harper & Brothers.
4. Stroud, W. D.: *The Diagnosis and Treatment of Cardiovascular Disease*, ed. 3, Philadelphia, 1945, F. A. Davis Company.
5. Taran, L. M., and Szilagyi, Nelly: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, *AM. HEART J.* **33**:14, 1947.
6. Bazett, H. C.: An Analysis of the Time Relations of the Electrocardiogram, *Heart* **7**:353, 1920.
7. Ashman, R., and Hull, E.: *Essentials of Electrocardiography*, ed. 2, New York, 1941, The Macmillan Company.

Clinical Reports

ISOLATED MYOCARDITIS IN NEWBORN AND YOUNG INFANTS

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MYOCARDITIS seems to be more common in children than in adults, even if epidemic diseases are not taken into account. Saphir,²⁰ for example, reported an incidence of 6.83 per cent in a post-mortem study of 1,420 children, whose ages ranged from 8 days to 16 years. During the same period of observation he found an incidence of 4.05 per cent in a post-mortem study of 3,712 adults.

Myocarditis is not uncommon in infancy, especially subsequent to infectious diseases, such as diphtheria, scarlatina, sepsis, typhus, rheumatic fever, and pneumonia. In all probability, it is more common at this age than has been recognized, because it is difficult to diagnose and, therefore, easily escapes attention unless roentgenograms and electrocardiograms are made routinely in all suspected cases.

In the majority of the cases that have been reported, myocarditis in newborn infants has been part of a general disease and has not been very significant in itself. An example is myocarditis associated with sepsis, emanating generally from the umbilicus or due to congenital syphilis.

Fetal endocarditis attracted much interest in earlier literature, and cases of fetal endomyocarditis also have been observed. These cases have given rise to the assumption that some cases of congenital defects of the heart are of inflammatory origin. Recent studies,^{1,10,20} however, have cast doubt upon this view.

Isolated myocarditis, a condition in which the cardiac findings are the only, or at least the dominating feature, seems to appear at any age. Its etiology is unknown. It is frequently difficult to diagnose clinically. It is often unrecognized, except at necropsy, and even then the disease usually is difficult to identify. Macroscopically, the heart is enlarged more or less conspicuously, but there is nothing else remarkable. Furthermore, the majority of pathologists emphasize the fact that a thorough histologic examination using a series of sections is often necessary before the changes can be recognized. In the

From a lecture read before the Swedish Society of Internal Medicine, March, 1947.

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more acute cases these changes consist of infiltration of the interstitial tissue by lymphocytes, plasma cells, leucocytes, and in some places, by eosinophiles. Degeneration of the muscle fibers of varying degrees of severity has also been noticed, and in long-standing cases an increase of the interstitial tissue is present.

Isolated myocarditis has been observed in a few instances among children in infancy. A review of such cases was published recently by Saphir and his associates²⁰ and by Keller.¹⁵ It seems to be rather rare among newborn infants. Saphir,²⁰ who bases his opinion on a study of the literature and on the examination of the hearts of newborn babies, asserts that except for myocarditis due to congenital syphilis, fetal or congenital myocarditis is extremely rare, if not nonexistent.

In the literature there are a few case reports of newborn and young infants with myocardial changes that are interpreted as congenital. In no case, however, can the arguments brought forward to support such an interpretation be considered convincing. One case of calcification of the myocardium with slight inflammatory changes was interpreted by Jacobsthal¹⁴ as congenital myocarditis. Opinions differ as to the correctness of Jacobsthal's interpretation, and Hart,¹¹ among others, asserted that the inflammatory changes observed by Jacobsthal were more probably reactive ones due to the calcification. Iff¹³ and Diamond⁵ also report cases of calcification of the muscular tissue of the hearts of newborn infants, in which cases the tissue exhibited degenerative changes but no signs of inflammatory processes.

In some cases of myocarditis among children about 6 months old,^{9,11} in which congenital genesis was assumed, such a long time had elapsed between birth and death that the findings cannot be considered convincing.

In the last few years paroxysmal tachycardia has been observed rather frequently among newborn and young infants, and one might believe myocarditis to be the provoking cause in some cases, as seems to be the case with older children. Also for that form of the disease in which pre-excitation exists, it has been thought possible that myocarditis can cause the disturbance in rhythm.^{3,18} In most cases of paroxysmal tachycardia occurring at this very early age, it has not been possible to recognize any causative heart disease or provoking factor; the hypothesis advanced has been that there may be a defective central and autonomous regulation of the activity of the heart during early infancy. Only in one instance¹⁹ have myocardial changes been detected, and in this case they were localized to the right auricle.

It is also noteworthy that in three cases of auricular flutter in newborn infants, the arrhythmia existed prior to delivery; this was also the case with one instance of auricular fibrillation and paroxysmal tachycardia.

Finally, in the heterogeneous group, idiopathic hypertrophy of the heart, a number of cases are reported with inflammatory changes in the myocardium.^{2,16,17} The histologic pictures resembled mild nonspecific pancarditis, and the possibility of an intrauterine infection or toxemia has been suggested. However, none of these infants was under 6 months of age.

Thus, cases of isolated myocarditis and what were believed to be sequelae to intrauterine myocarditis have been found in infants. However, one link in the chain is missing, namely, verified myocarditis in fetuses or newborn infants.

During the last six months we have had the opportunity of studying a number of cases of myocarditis among newborn and very young infants. The cases demonstrate various different types of the course of the disease among infants and show that the disease is in all probability not uncommon and is of practical significance. As we have pointed out, myocarditis is difficult to diagnose, and even though heart disease was established in the majority of our cases, a complete diagnosis was not possible before autopsy or even before a microscopic examination of the heart had been made. Three of the infants showed paroxysmal tachycardia. In none could the etiology of the disease be explained. They must be described as cryptogenic. In two newborn infants the myocarditis was probably congenital, although no proof of such a genesis can be produced.

CASE REPORTS

CASE 1.—(Norrtull's Hospital, F 675/46.) The patient was a 9-day-old girl without any significant family history. The 37-year-old mother was a secundipara and her first child was 4½ years old and healthy. Previously the mother had been generally healthy except for a non-toxic goiter that had never given trouble. While pregnant with our patient she had felt constantly tired and two months before term had been treated for bilateral maxillary sinusitis. She could not remember having had fever. She showed no signs of toxemia due to pregnancy; the blood pressure was normal and there was no albuminuria.*

The delivery was normal. The baby weighed 3.76 grams at birth. During the first few days the child appeared to be healthy and nursed well. Three or four days after birth, however, she began to appear sluggish and to lose her appetite. On the ninth day there was a sudden decline in the health of the infant and after vomiting, she became cyanotic. On examination the rate of the heart was found to be 300 beats per minute. The child was transferred immediately to the Children's Hospital. On her arrival at Norrtull's Hospital, she was in poor condition. She was obviously cyanotic, had cold hands and feet, and had edema localized to the inferior part of the legs and the feet. The liver was palpated three fingerbreadths below the costal margin. On auscultation of the heart no definite murmurs were heard. The electrocardiogram showed what was considered to be a sinus tachycardia with a rate of about 300 per minute and pronounced right-sided preponderance. A radiograph of the heart showed a conspicuous enlargement of the left ventricle without lung stasis. The morning after admission to the hospital, the electrocardiogram showed low voltage complexes and the cyanosis had increased; the child was breathing only with effort. The heart rate was still around 300. During the course of the day she became still worse and appeared to be dying. On admission to the hospital she had been given 0.125 mg. of neostigmine, which had had no effect. Three drops of *Digitol* were given three times, which is about equivalent to 7.5 mg. of *digitalis folia*. A further injection of neostigmine was then administered and return to normal heart rate occurred immediately. The result was a marked clinical improvement. The heart rate fell to 125. The electrocardiogram no longer showed low voltage, but a few extrasystoles were present. Conduction time was normal. The patient continued to improve for ten hours, after which sudden death occurred during the night without any previous signs of its approach.

Post-mortem examination revealed moderate enlargement of the heart, the heart weighing 30 grams (normal weight, 20, or at most, 25 grams). The heart was dilated and flabby. There were no abnormalities in the endocardium or coronary arteries. The myocardium was slightly

*Wassermann reaction was negative.

spotted. The lungs were rather large, hyperemic; and extremely edematous. The spleen weighed 14 grams and the kidneys, 43 grams. The liver was mottled and congested. It weighed 125 grams.

Histologically, there was observed a pronounced interstitial myocarditis (Fig. 1), especially in the left ventricle, but also in the other parts. The myocarditis was characterized by degenerative changes with fatty degeneration and atrophy of the muscular fibers. There was interstitial edema and infiltration mainly by lymphocytes but also by polymorphonuclear cells and a few plasma cells, eosinophiles, and epithelioid cells. There were no vascular changes. Staining for spirochetes by Levaditi's method gave a negative result. The liver and the spleen showed pronounced chronic congestion with central atrophy in the liver lobules.

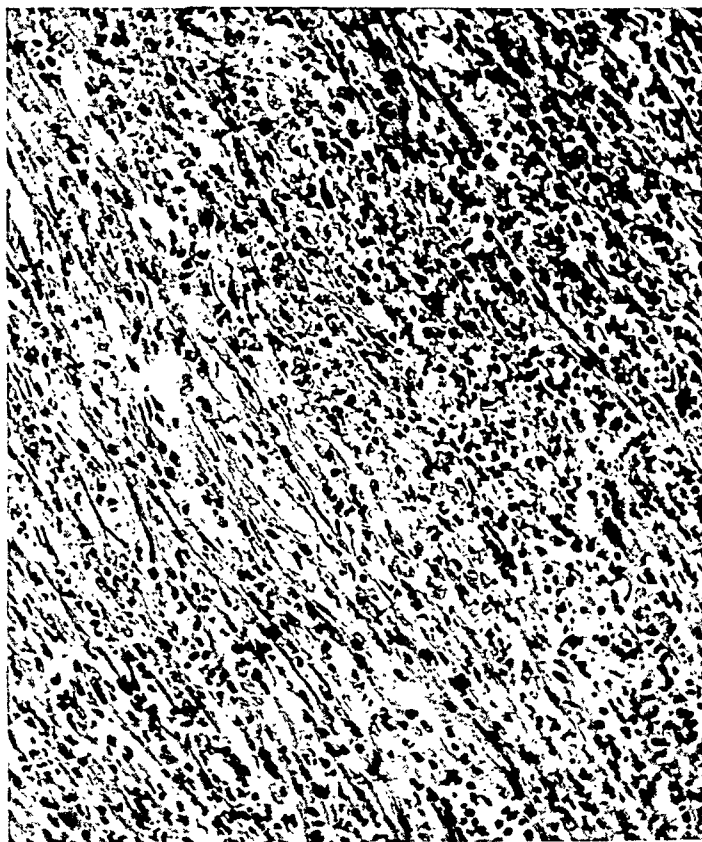


Fig. 1.—Section from myocardium of patient in Case 1 ($\times 120$).

CASE 2.—(Crown Princess Lovisa's Hospital, 1256/46.) This case was very similar to Case 1. The infant's parents were healthy. Pregnancy and delivery were normal. The first few days after birth the boy seemed to be healthy, but on the fifth day he became acutely ill with cyanosis and shallow, hasty breathing, for which reason he was transferred to the hospital, where he died shortly after admission. Unfortunately, there is no report of the heart rate, and because of the poor condition of the infant it was impossible to take an electrocardiogram or a roentgenogram.

Post-mortem examination revealed the same pathoanatomic picture as in Case 1. The heart weighed 35 grams. It also displayed mild fibrinous pericarditis. In the left auricle there was a small, partly organized blood clot. The spleen weighed 25 grams; the kidneys, 11 grams; and the liver, 186 grams.

The two following cases originate from the children's wards of country hospitals and were sent in for pathoanatomic examination. With the kind permission of these hospitals, they will be reported briefly.

CASE 3.—(Boden.) The patient was a 3-week-old baby whose illness started with sudden collapse and extreme tachycardia. The infant was admitted to the Children's Department of the hospital, where he died after twenty-four hours. *Histologically*, the heart finding was, on the whole, similar to that of Case 1, but the changes were not so pronounced and were localized to the left ventricle. Etiology was unknown.

CASE 4.—(Norrköping.) The fourth patient was a baby boy who at the age of $2\frac{1}{2}$ months showed evidence of paroxysmal tachycardia. The infant died at the age of $4\frac{1}{2}$ months. A *post-mortem examination* showed that the heart was considerably enlarged, the weight being 60 grams. Microscopic examination in this instance revealed a preponderantly chronic myocardial process with fibrosis, which, judging by appearances, seemed to be of inflammatory genesis without any signs of the scars being caused by changes in the blood vessels.

The myocardial changes in the first two cases do not in themselves give any direct guidance with respect to age. The fairly severe hypertrophy of the heart, the marked stasis and mottling of the liver, and the plainly evident organization of the thrombus in the auricle in the one case furnish, on the other hand, a certain amount of evidence on this point. Nor is it possible to determine the exact age of these changes, but it is not very probable that the hypertrophy of the heart and the high degree of liver stasis, in particular, could have reached such a stage of development if the myocarditis had arisen after birth. Therefore, we have nothing to prove that the myocarditis had been present before birth, but the circumstances at hand are evidence for, rather than against, the assumption that congenital myocarditis was present.

Finally, a case may be mentioned that might well be considered isolated myocarditis in a newborn infant, and with the child surviving the disease.

CASE 5.—(Norrtull's Hospital, F 307/47.) On the first day of life the infant in question, a girl, suffered from repeated attacks of cyanosis and, therefore, was admitted to Norrtull's Hospital. The history contained nothing of interest from the standpoint of heredity. The mother had been healthy during pregnancy and the delivery was normal. On arrival at the hospital, the infant was severely affected. Her face was pale and gray, and she had pronounced dyspnea, without fever. On auscultation of the heart a gallop rhythm was audible. A roentgenogram of the thorax exhibited a conspicuously enlarged heart. Another positive physical finding was an enlarged liver of increased firmness, the lower margin of which extended one fingerbreadth below the costal margin. The child was placed in an oxygen incubator but recovered only slowly. For the first few days she was given penicillin and strong stimulants, without any visible effect. After a week the child began to nurse by herself after previously having been nourished by means of a stomach tube. The gallop rhythm disappeared. The first heart sound was very faint and indistinct, but after another week it recovered its normal tone. It was not until two weeks later that the child could manage without extra oxygen, and after six weeks the weight curve began to rise. After seven weeks the child was discharged from the hospital. Apart from the circulatory signs, no anomalous changes could be detected, and in particular, there were no signs of other infectious processes or intracranial lesions.

During the stay of the patient at the hospital, the volume of the heart varied as shown in Table I.

The child thus began to suffer from severe cyanotic attacks soon after birth and the subsequent serious course of the disease was dominated also by dyspnea. The heart findings were temporary tachycardia with gallop rhythm; there was considerable enlargement of the heart and liver, which organs recovered normal size simultaneously; and there were transient electrocardiographic changes with prolongation of the P-Q and Q-T time, initial flattening and thereafter inversion of the T waves in the standard leads with ultimate recovery.

TABLE I. THE VARYING VOLUME OF THE HEART IN CASE 5

DAY AFTER BIRTH	VOLUME (ML.)	ML. PER KG. OF BODY WEIGHT
Second	67.5	19.3
Sixth	74	20.6
Twenty-second	34	11.6
Thirty-seventh	35	11.3
Sixty-seventh	62	12.8

The electrocardiogram showed changes as given in Table II.

The five cases which have been presented constitute various types and stages of isolated myocarditis among newborn and young infants. Of the five infants, three had paroxysmal tachycardia. Greatest interest is naturally attached to those cases in which myocarditis was probably congenital.

TABLE II. ELECTROCARDIOGRAPHIC CHANGES IN CASE 5

AGE (DAYS)	RATE (PER MIN.)	P-R INTERVAL LEAD II (SEC.)	Q-T INTERVAL LEAD II (SEC.)	T WAVE			ELEC- TRICAL AXIS
				LEAD I	LEAD II	LEAD III	
2	160	0.12		Isoelectric	Positive	Positive	140°
4	150	0.12	0.22	Isoelectric	Slightly positive	Slightly positive	140°
16	125	0.13	0.30	Negative	Negative	Slightly positive	
23	172	0.14		Isoelectric	Isoelectric	Slightly negative	120°
30	145	0.12		Isoelectric	Isoelectric	Slightly negative	100°
40	130	0.10	0.26	Positive	Positive	Slightly negative	80°
67	160	0.11	0.24	Well-developed		Negative	80°

SUMMARY

Five cases of isolated myocarditis among newborn and young infants are described. Four infants died and were subjected to post-mortem examination. The cases represent various types and stages of the disease. Three of the infants had paroxysmal tachycardia. In two, myocarditis was probably congenital. The cause of the disease could not be explained in any of the cases.

REFERENCES

1. Axén, O., and Lind, J.: Roentgenologic Determination of Heart Volume in Infants, *Acta paediat.* 32:270, 1945.

2. Benjamin, B., and Simon, M. A.: So-called Congenital Idiopathic Hypertrophy of the Heart, *Am. J. Dis. Child.* 59:842, 1940.

3. Christensen, J. F.: Paroxysmatisk tachycardi hos spæde børn, *Nord. med.* 22:797, 1944.

4. Cosgrave, G. E., and Kaump, D. H.: Endocardial Sclerosis in Infants and Children, *Am. J. Clin. Path.* 16:322, 1946.

5. Diamond, M.: Calcification of the Myocardium in a Premature Infant, *Arch. Path.* 14:137, 1932.

6. Dorsch, G.: Die Herzmuskelentzündung als Ursache angeborener Herzcyanose, *Diss. Erlangen*, 1855.

7. Feldmann, R.: Myocarditis und Endocarditis in Säuglingsalter, *Jahrb. f. Kinderh. (ann. paediat.)* 150:138, 1938.
8. Frisell, E.: Zur Frage der paroxysmalen Tachycardie und des Herzflatterns in der ersten Lebenswoche, *Acta paediat.* 34:30, 1947.
9. Froboese, C.: Fibrosis myocardii congenita (angeborenes Schwielenherz) oder Säuglings-myokarditis, *Virchows Arch. f. Path. Anat.* 284:861, 1932.
10. Gross, P.: Concept of Fetal Endocarditis: A General Review With Report of an Illustrative Case, *Arch. Path.* 31:163, 1941.
11. Hart, C.: Die Herzmuskelverkalkung, *Frankfurt. Ztschr. f. Path.* 3:706, 1909.
12. Hertz, M.: Demonstration at Sectionspraeparat af formentlig medfødt Dilatation og Hypertrofi af Cor, *Nord. med.* 17:260, 1943.
13. Iff, W.: Ueber angeborene Verkalkungen, besonders der Arterien, *Virchow's Arch. f. path. Anat.* 281:377, 1931.
14. Jacobstahl, H.: Verkalkung von Herzmuskelfasern bei einem Kinde, *Virchow's Arch. f. path. Anat.* 159:361, 1900.
15. Keller, H.: Ueber idiopathische Myocarditis in Kindesalter und ihre Differentialdiagnose, *Helvet. paed. acta* 1:57, 1945.
16. Kenny, F. E., and Sanes, S.: Dilatation and Hypertrophy of the Heart in Infancy Due to Parenchymatous Myocarditis, *J. Pediat.* 3:321, 1933.
17. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children, With Myocardial Degeneration and Fibrosis (So Called Congenital Idiopathic Hypertrophy), *Am. J. Dis. Child.* 45:828, 1933.
18. Lind, J.: Preexcitation of the Ventricular Part of the Heart and Its Occurrence in Children, *Acta paediat.* 32:153, 1945.
19. Piotti, A.: Die paroxysmale Tachycardie beim Kleinkind, *Cardiologia* 9:121, 1945.
20. Saphir, O., Wile, A., and Reingold, I. M.: Myocarditis in Children, *Am. J. Dis. Child.* 67:294, 1944.
21. Stiassny, S.: Ein Fall von angeborener Myokarditis fibrosa, *Zentralbl. f. allg. Path. u. path. Anat.* 12:417, 1901.
22. Willi, H.: Die akute Herzinsufficiens beim Neugeborenen, *Schweiz. med. Wchnschr.* 73:189, 1943.
23. Von Zalka, E.: Histologische Untersuchungen des Myokards bei kongenitalen Herzveränderungen, *Frankfurt. Ztschr. f. Path.* 30:144, 1924.

A DEVICE FOR MEASURING THE MEAN ELECTRICAL AXIS OF THE HEART

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IN 1913 Einthoven, Fahr, and De Waart¹ described a method for determining the manifest value and direction of the mean of the instantaneous electromotive forces produced by the heart throughout the QRS interval. The fundamental principles of the Einthoven equilateral triangle also were set forth in that publication. The vector quantity representing the mean of the instantaneous electromotive forces has been designated the mean electrical axis of the heart. The angle which the mean electrical axis makes with the horizontal, that is, the base of the equilateral triangle or a line representing Lead I, was designated by Einthoven as the angle alpha. A number of methods have been described by which the angle alpha may be determined. These include the chart of Carter, Richter, and Greene² and also that devised by Dieuaide.³ The triaxial reference system developed by Bayley⁴ has also proved useful. The accuracy of the Einthoven triangle and that of the assumptions upon which it is based have been questioned, but Wilson⁵ has pointed out that the error of this method is negligible so far as its practical applications are concerned.

In order to avoid the use of elaborate charts and to eliminate the need for preparing a separate diagram for each electrocardiogram being interpreted, a device has been prepared for determining the mean electrical axis which is an adaptation of the "Magic Slate."* This slate is marketed as a toy writing board. It consists of a supporting cardboard one of whose surfaces is dyed black and impregnated with a paraffin material. Over this there is a heavy, translucent, glossy paper and overlying this, a clear plastic sheet. When a line is drawn on the plastic sheet with a blunt-pointed, wooden stylus, the impression appears on the glossy sheet as a result of its compression against and adherence to the impregnated black cardboard. This impression is erased simply by lifting and separating the plastic and glossy sheets from the cardboard (Fig. 1). A diagram of the Einthoven triangle circumscribed by a circle graduated in degrees was drawn upon the glossy sheet in India ink. Perpendicular lines to the three sides of the triangle were also inscribed (Fig. 2). In order to use this diagram, the algebraic sum of the areas of the Q, R, and S deflections of any two of the three standard leads is determined and the appropriate number of

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*Manufactured by the Strathmore Company, Aurora, Ill.

spaces is counted on the proper side of the respective lead line. Perpendicular lines are drawn from the points thus determined into the triangle until they intersect. A third line is then drawn from the central point of the triangle, O , through this point of intersection and extended to the circle which circumscribes the triangle. That point on the circle intersected by the extended line represents the angle α expressed in degrees. The magnitude of the mean electrical axis is represented by the length of the line from the central point O to the intersection of the perpendicular lines from the sides of the triangle. The mean electrical axis thus determined is erased by simply separating the glossy sheet from the underlying cardboard and the device is then ready for use again.

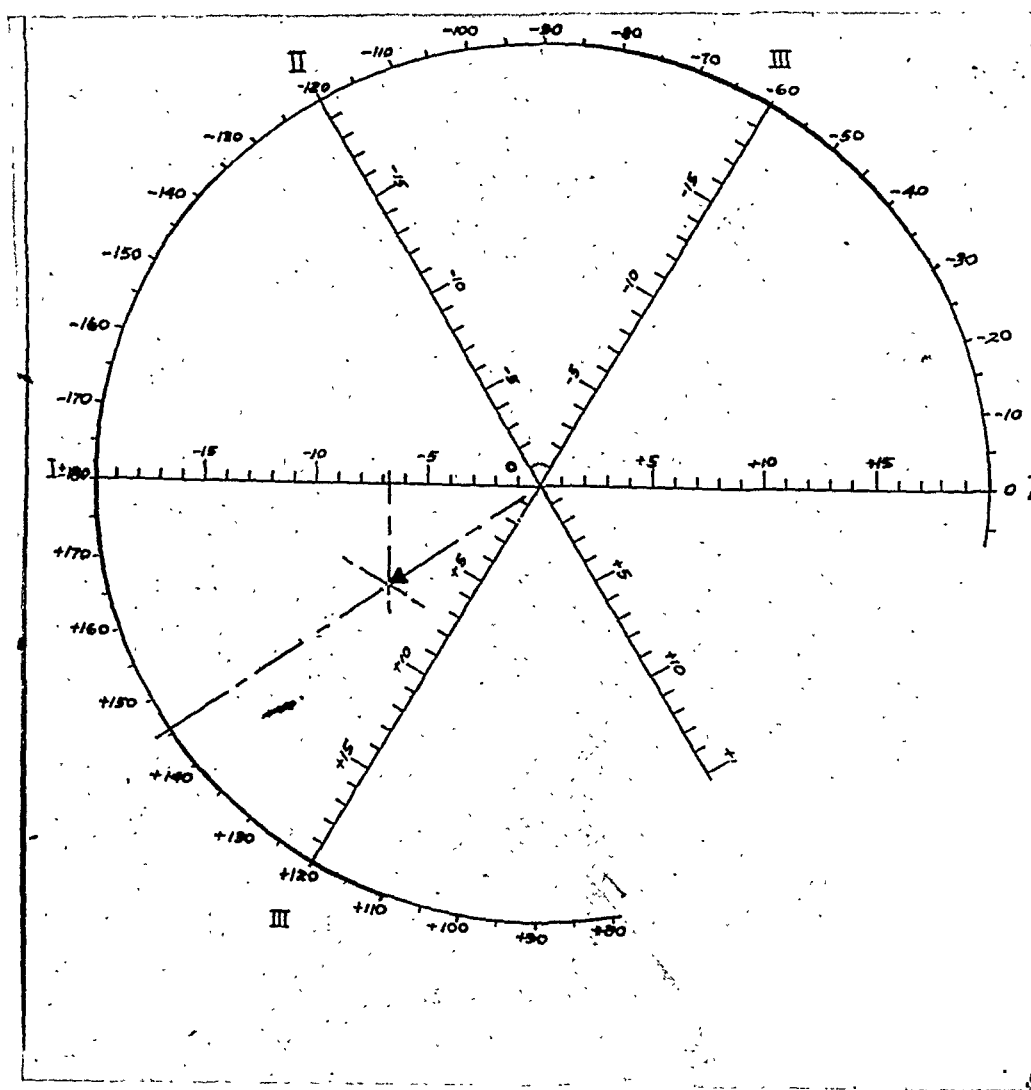
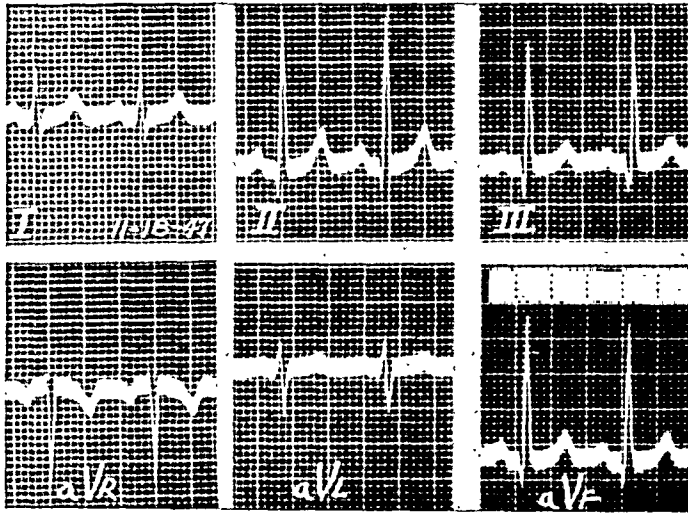
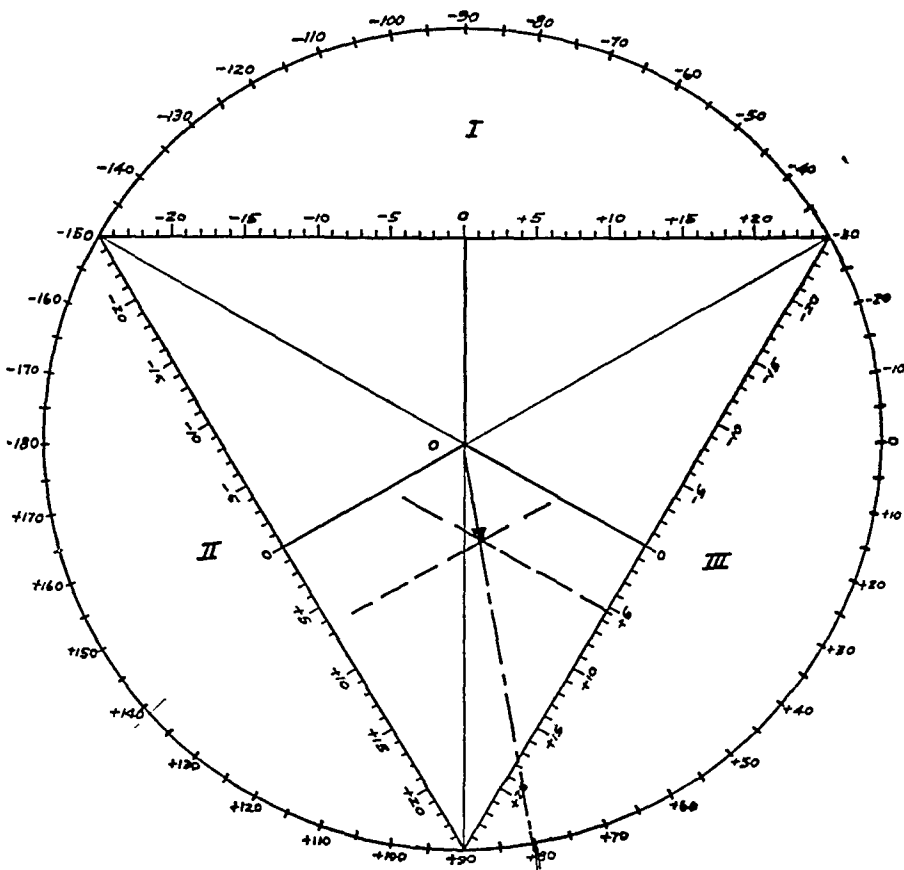


Fig. 1.—Photograph of "Magic Slate" as modified for use in determining the mean electrical axis. The clear plastic sheet, which is uppermost, and the translucent glossy sheet beneath it, have been turned back at the lower right-hand corner to reveal the black, paraffined board backing. In this preparation the tri-axial reference system has been inscribed upon the glossy second sheet. The determination for a case of marked right axis deviation ($+146^\circ$) is shown. To erase, the clear and the translucent sheets are simply lifted up from the backing.



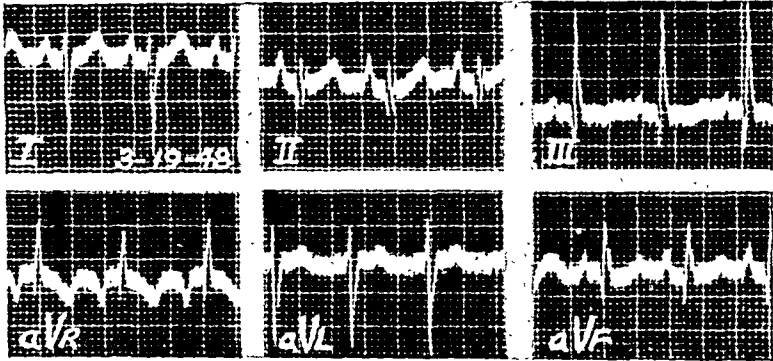
A.



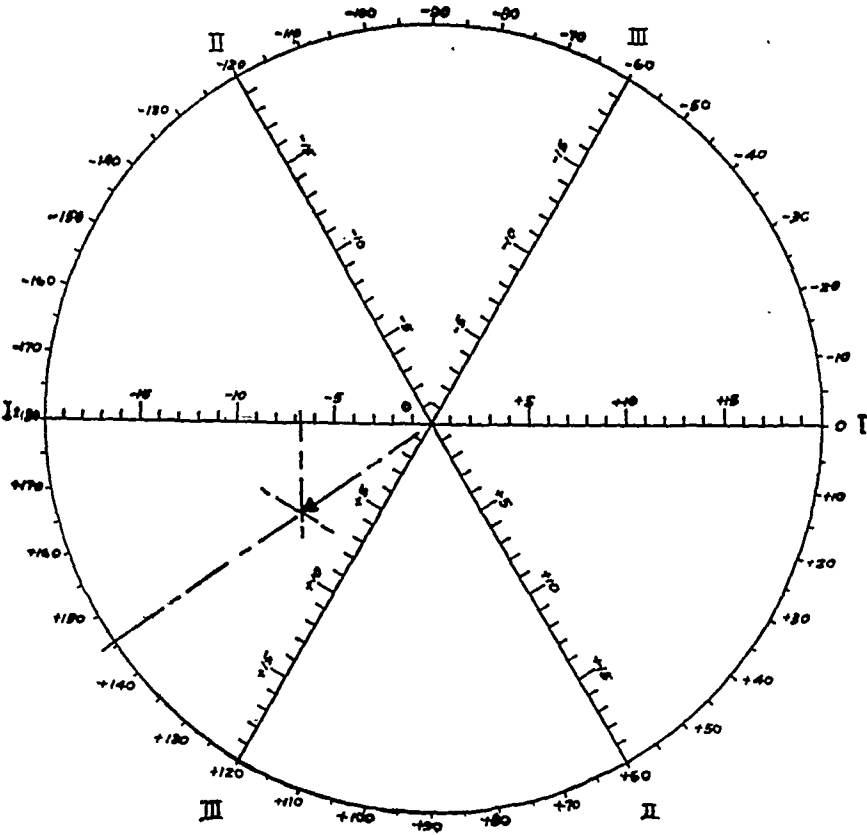
B.

Fig. 2.—A, Standard and unipolar limb leads from a 13-year-old girl with possible rheumatic fever. The area of QRS is +14 units in Lead I, +63 units in Lead II, and +52 units in Lead III.

B, Photograph of mean electrical axis as determined upon the "Magic Slate" preparation with Einthoven triangle inscribed upon the translucent sheet. Mean electrical axis is +81 degrees.



A.



B.

Fig. 3.—A, Standard and unipolar limb leads from a 5-year-old boy with the tetralogy of Fallot. The area of QRS is -34.5 units in Lead I and $+36$ units in Lead III.

B, Photograph of mean electrical axis as determined upon the "Magic Slate" preparation with tri-axial reference system inscribed upon the translucent sheet. Mean electrical axis is $+146$ degrees. Area units have been doubled to facilitate measurements so that -6.9 units have been marked off on the I-I axis and $+7.2$ units marked off on the III-III axis.

A similar construction using the triaxial reference system of Bayley⁴ has also been prepared (Fig. 3). The algebraic sum of the areas of the Q, R, and S deflections in any two of the three standard leads may be determined and applied to the figure along the axis of the proper lead. Perpendicular lines are then drawn from the leads so employed until they intersect. A line is then drawn from the center of the reference system, *O*, through the intersection of the perpendicular lines and extended to intersect the circle. Then, as in the first construction, the angle alpha is simply read, in degrees, at the point of intersection. Examples illustrating the use of both constructions are shown (Figs. 2 and 3). If the electrocardiographic areas are larger than the units designated on the diagram they can be reduced by an appropriate fraction.

The mean electrical axis of the heart is most accurately determined by estimating the electrocardiographic area of each of the elements of the QRS complex rather than by using merely the size of the Q, R, or S deflections in each of the various leads employed. The electrocardiographic areas can be estimated by multiplying the height of each individual deflection by one-half the width of its base, in the manner described by Ashman and Byer.⁶

SUMMARY

A device helpful in determining the mean electrical axis of the heart has been described. It employs the "Magic Slate," which is commercially available as an inexpensive toy.

This device can be used repeatedly and it has greater flexibility than other more elaborate charts now available.

It must be borne in mind that the mean electrical axis of the heart is influenced by several factors other than the relative weights of the two ventricles. Chief among these are the position of the heart and the status of intraventricular conduction.⁷

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* **150**:275, 1913.
2. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* **30**:162, 1919.
3. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, *Arch. Int. Med.* **27**:558, 1921.
4. Bayley, R. H.: On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, *AM. HEART J.* **26**:769, 1943.
5. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, *AM. HEART J.* **32**:277, 1946.
6. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient. I. Factors Which Affect Its Direction and Its Relation to the Mean QRS Axis, *AM. HEART J.* **25**:16, 1943.
7. Wilson F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, *Advances in Internal Medicine*, vol. II, New York, 1947, Interscience Publishers.

Abstracts and Reviews

Selected Abstracts

Wilson, M. G., Payson, J. W., and Lubschez, R.: Experience of Rheumatic Patients Who Served in the Armed Forces, 1942-46. Am. J. Pub. Health 38:398 (March), 1948.

Of 268 rheumatic patients of military age in the New York Hospital Children's Clinic, 62 per cent (167) were accepted for the Services. One hundred one patients were classified as 4F (physically unfit for military duty). In the Service group, 23 per cent had had one or more attacks of active carditis with failure. In about one-half of the Service group and one-third of the civilian group, the physical signs of valvular lesions had regressed. In the civilian group the past rheumatic history was more severe and the resultant cardiac damage was of greatest degree. In this group 43 per cent had had one or more attacks of active carditis with failure during childhood.

The incidence of rheumatic fever among the patients in military service revealed that three men were hospitalized for rheumatic fever while in the Armed Forces. In the civilian group during 402 patient-years, there were seven patients with recurrent attacks, one of whom died. In addition, two patients had bacterial endocarditis and two developed auricular fibrillation. It is noteworthy that cardiac failure, bacterial endocarditis, and auricular fibrillation did not occur among the men in the Service. Of particular importance is the observation that among the men who returned to the clinic after discharge, no change in physical signs or cardiac enlargement was observed. The authors state that in their experience the risk of a recurrent attack of rheumatic fever is no greater while in the Services than while in civilian pursuits.

BELLET.

Rabinovitch, R., Elliott, K. A. C., and McEachern, D.: Cytochrome C: Intravenous Administration in Man. J. Lab. & Clin. Med. 33:294 (March), 1948.

Cytochrome C was administered intravenously in doses of 50 to 512 mg. daily for periods up to thirty-one days. Subjects included one normal individual and eight patients with various diseases. The concentration was determined by the spectrophotometric method described by Rosenthal and Drabkin.

Injections of 50 to 500 mg. of cytochrome C, administered intravenously at intervals of one week to the one normal adult, and single doses of 500 mg., administered to two patients suffering from neuromuscular disease, caused no subjective symptoms. No changes were noted in pulse, respiration, blood pressure, temperature, or basal metabolism for three hours following injection.

Eight patients suffering from various neuromuscular disease and one normal control were given daily intravenous doses of cytochrome C which varied from 50 to 500 milligrams. No detectable changes in symptoms or signs were produced. The substance was not detected spectroscopically in the serum of these patients except where blood samples were collected within thirty minutes after injection of single doses of 500 milligrams.

KLINE.

Green, D. M., Johnson, A. D., Lobb, A., and Cusick, G.: The Effects of Adrenalin in Normal and Hypertensive Patients in Relation to the Mechanism of Sustained Pressure Elevations. J. Lab. & Clin. Med. 33:332 (March), 1948.

Eighty continuous infusions of adrenalin in a concentration of 1.0 mg. per cent were administered to thirty-nine men and twelve women whose blood pressures ranged from 90 to 246 systolic and from 55 to 126 diastolic. During the administration of saline, pulse rate and blood pressure values were determined before, during, and for twelve hours after each infusion. When the undiluted solution reached the circulation, the systolic and occasionally the diastolic pressure rose above the preinfusion value. An increase in the rate of administration produced a further rise in systolic and diastolic pressures to a new maximum in one to three minutes. Following cessation of infusion, both systolic and diastolic pressures dropped abruptly. A minimum level was reached usually by ten and not later than fifteen minutes after clamping of the infusion tubing. These minimum levels were lower than the initial blood pressure levels in all but one instance and were accompanied by cardiac acceleration. Daily infusion on the same subject produced almost identical blood pressure responses. However, increase in the subjective limit of tolerance was marked.

The authors found that in general the higher the patient's initial pressure the farther the pressure dropped below the initial level when the infusion was stopped. In a number of instances the minimum pressures developed within the range usually associated with shock. The depression of pressure in association with evidences of vasodilatation suggests a temporary persistence of compensatory vasodepressor activity, either nervous or humoral.

It was found that the tolerance to adrenalin was inversely proportional to the initial blood pressure. One subject in the series complained of mild substernal pain which subsided without sequelae when the infusion was stopped. Cardiac irregularity, due to premature contractions, occurred to some degree in nearly all patients. In one instance it was sufficiently marked to dictate the cessation of the infusion. Three persons developed cerebral symptoms, characterized in one by intense headache and momentary syncope, in another by transient unconsciousness, and in a third by a hemiplegic syndrome without loss of consciousness, from which recovery was complete in twelve hours. These alarming episodes which occurred during the latter phase of these studies influenced their termination.

The correlation between the height of the initial pressure and the depth of the subsequent postinfusion depression provides additional data to indicate that the vasodilator capacity of the hypertensive individual is enhanced rather than diminished. The accumulated evidence demonstrates the availability of compensatory mechanisms in the hypertensive subject and the capacity of the vascular apparatus to respond effectively when these mechanisms are properly stimulated.

KLINE.

Selzer, A.: The Immediate Sequelae of Myocardial Infarction. Their Relation to the Prognosis. Am. J. M. Sc. 216:172 (Aug.), 1948.

A series of 130 unselected cases of recent myocardial infarction found at autopsy was examined. In thirty-five patients, myocardial infarction was a terminal event in otherwise seriously ill patients and was regarded as of little clinical interest. The remaining ninety-five patients were apparently well prior to the onset of the myocardial infarction and were subjected to detailed analysis as "primary" myocardial infarction.

The immediate cause of death in this group of ninety-five cases was: progressive circulatory failure, with or without shock, in twenty-eight cases; sudden death due to arrhythmia in twenty-four cases; embolic phenomena in fifteen; cardiac rupture in eight; and secondary coronary thrombosis in five cases. In the remaining fifteen cases death was due to incidental complications not related to myocardial infarction.

No significant correlation was found between the age of the patients, the degree of the coronary arteriosclerosis, the size of the infarction, and the presence of myocardial scars and of cardiac hypertrophy, on one hand, and the course, the duration of illness, and the frequency of complications, on the other hand. This is interpreted as indicating the adequacy of circulatory adjustment even in cases with extensive damage to the heart.

The prognosis of acute myocardial infarction is unpredictable because the importance of cardiac insufficiency, the direct consequence of the damage to the myocardium, is outweighed by secondary complications. The number of patients who die immediately is twice, or perhaps three times greater than the estimated number of patients who develop irreparable cardiac damage. The important sequelae of myocardial infarction, which can be considered potentially preventable causes of death, are serious arrhythmia, thromboembolic phenomena, and shock.

DURANT.

Flaxman, N.: Digitoxin Poisoning. Report of 30 cases. Am. J. M. Sc. 216:179 (Aug.), 1948.

In thirteen months digitoxin poisoning was seen in thirty patients who had received the regularly prescribed doses of this isolated digitalis glycoside. The age and sex of the patient or the type of underlying heart disease had no relation to the occurrence of the poisoning. Symptoms, such as are known to be due to digitalis overdosage, occurred infrequently in these patients. Signs of disorders of the cardiac mechanism, especially the more serious conduction disturbances, were the earliest and most frequent clinical and electrocardiographic manifestations.

Considerable caution should be exercised in the administration of the digitoxin preparations in the regularly advised dosage and form to any patient suffering with congestive heart failure, because the action may be rapidly intoxicating to the cardiac musculature and its conduction system. The factor of safety for this particular digitalis purpurea glycoside seems to be extremely narrow.

DURANT.

DeMuth, W. E., and Rawson, A. J.: Pseudomonas Septicemia and Endocarditis. Report of a Case. Am. J. M. Sc. 216:195 (Aug.), 1948.

A case is reported of protracted sepsis by *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) with lesions in many organs and massive acute endocarditis involving the aortic valve. Only one other case of endocarditis of the aortic valve caused by this organism has been found in the literature.

DURANT.

Thompson, J. L., Jr., and Kistin, A. D.: Hoarseness in Heart Disease. Ann. Int. Med. 29:259 (Aug.), 1948.

Two cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis are reported. In one, a 30-year-old man who died following an attack of acute rheumatic fever, necropsy showed minimal scarring of the mitral valve and only slight enlargement of the left auricle. The other was a 31-year-old man in whom angiocardigraphic studies revealed considerable enlargement of the left auricle. Common to both cases was dilatation of the pulmonary artery. Because of the peculiar anatomical relations between the left recurrent laryngeal nerve and the pulmonary artery and aorta, the dilatation of the pulmonary artery was considered to be responsible for the left vocal cord paralysis noted in the two cases. The authors also suggest that there may be another but unknown factor contributing to the left recurrent laryngeal nerve paralysis in view of the large number of cases with comparable dilatation of the pulmonary artery which do not exhibit pressure effects upon the nerve. The many reports dealing with the subject of recurrent laryngeal nerve paralysis in heart disease are also reviewed and analyzed.

WENDKOS.

Altshuler, S. S., Hoffman, K. M. and Fitzgerald, P. J.: Electrocardiographic Changes in Diphtheria. Ann. Int. Med. 29:294 (Aug.), 1948.

In the American Zone of Germany, 600 patients with proved diphtheria were seen from September, 1945, to December, 1946. This number included twenty-six cases of cutaneous diphtheria. The youngest patient was 18 years of age, the oldest was 43, and the average age was 23.4 years. An electrocardiogram was recorded as soon as diphtheria was suspected clinically or when a positive culture was reported. Thereafter, electrocardiograms were recorded at weekly intervals or more often when indicated.

Of the 600 cases of diphtheria studied, 143 (23.9 per cent) presented electrocardiographic changes at some time during hospitalization. Flattening or inversion of the T waves occurred in 108 cases. In over 50 per cent of this number, the T-wave abnormalities were present in three or more leads. T-wave abnormalities persisted for from two, to longer than twenty-three weeks.

Two patients developed right bundle branch block. Deep inversion of all the T waves followed the temporary bundle branch block pattern. The electrocardiogram was not within normal limits after eighteen weeks in one of these patients, nor after twenty-three weeks in the other patient. Prolongation of the P-R interval occurred in eleven patients. The commonly held opinion that prolongation of the P-R interval is the most common abnormality in diphtheritic infections was not substantiated by this study. Two patients developed complete heart block without a preliminary period of lesser degrees of A-V heart block. Of these two patients with complete A-V heart block, the electrocardiogram in one returned to normal after six weeks, whereas it returned to normal after ten weeks in the other patient. Recovery was uneventful in both cases.

The study of these 600 patients permits the general observation that if a patient with diphtheria has not shown electrocardiographic changes by the end of the fourth week after the onset of his clinical infection, the possibilities of myocardial involvement from the disease are few.

No correlation was possible between the severity of the infection and the severity of the electrocardiographic changes. The patients with the most marked and prolonged abnormalities usually had clinically severe infections but some patients with mild infections who were asymptomatic after the first few days had marked and persistent electrocardiographic changes.

WENDKOS.

Sweeney, J. S., and Pace, J. M.: Hypertension Caused by Unilateral Kidney Disease (A Follow-Up Report). Ann. Int. Med. 29:370 (Aug.), 1948.

Twelve days following the removal, in a 21-year-old woman, of a diseased shrunken right kidney due to antecedent pyelonephritis, the systolic blood pressure level fell from 240 mm. to 126 mm., the diastolic blood pressure level fell from 140 mm. to 78 mm., and the hypertensive papilledema receded completely. Seven years following the operation, the systolic blood pressure averaged 118 mm. and the diastolic pressure 82 millimeters. The patient in all respects appeared to be normal. The authors consider these findings to be conclusive evidence that an occasional case of severe hypertensive disease may be benefited by removal of a diseased unilateral kidney.

WENDKOS.

White, J. C., Heroy, W. W., and Goodman, E. N.: Causalgia Following Gunshot Injuries of Nerves. Ann. Surg. 128:161 (Aug.), 1948.

The authors present a study of thirteen patients suffering from causalgia as a result of gunshot injuries of nerves. It is their opinion that this term should be limited to include only the sequelae to penetrating wounds of the extremities which cause injury to the nerve trunks and the triad of burning pain, trophic changes, and autonomic phenomena. They also call attention to the fact that vasodilatation is certainly not a constant finding in this clinical entity, although it is possible that this sign is present early in the disease.

The authors noted that the pain in causalgia is aggravated to an unbearable degree by factors which increase sympathetic discharge from the hypothalamic centers, such as thermal and psychic stimuli. Therefore, interruption of the sympathetic outflow, as by preganglionic sympathectomy, is an effective method of treatment and should be performed at an early date. In the authors' cases sympathectomy resulted in consistent relief of the burning pain. It was their impression that this procedure resulted in elimination of efferent sympathetic discharge from the hypothalamic centers rather than in any interruption of pain fibers. The recent work on animals, suggesting that there may be a short-circuiting effect in the area of the injured peripheral nerve which permits direct irritation of sensory afferent fibers by efferent sympathetic impulses, is presented in support of their view.

ABRAMSON.

Keeley, J. L.: Saddle Embolus of the Aorta: Report of Successful Embolectomy.
Ann. Surg. 128:257 (Aug.), 1948.

The author reports an additional successful embolectomy at the bifurcation of the aorta. This occurred in a woman 52 years of age recovering from congestive heart failure and also suffering from auricular fibrillation. The diagnosis was made on the basis of sudden onset of paralysis of both feet, severe pain, coldness, and numbness. Pulsations in the abdominal aorta could be felt, but none were present below the level of the sacral promontory. Embolectomy was performed six hours after the onset of symptoms. An obstructing mass of clot was removed from the region of the bifurcation, together with a tail thrombus about six inches long from the right iliac artery and a segment from the left. Immediately after operation, pulsations could be felt in all peripheral arteries except the left dorsalis pedis. Subsequently this vessel also developed pulsations. The only aftereffects were edema of the left leg, which lasted for six weeks, and some persistent weakness of the left peroneal muscles.

With regard to diagnosis, two general types of histories have been obtained in proved cases. One is characterized by sudden localized pain, indicating approximately the point at which the embolus has been arrested, and, after an interval lasting up to several hours, a diffuse type of aching pain throughout the portions distal to the obstruction. The latter is due principally to anoxia of the muscle. This clinical picture can be explained on the basis of occlusion of the main artery accompanied by vasospasm of vessels distally, with subsequent thrombus formation blocking the collateral circulation. The other mode of onset consists of paresthesia as the initial symptom, followed by numbness, diffuse pain, and paralysis as anoxia becomes more severe.

Although the absence of pulsations is the most important sign, this finding should be carefully evaluated. Vasospasm may be so severe as to obliterate pulsations in vessels not obstructed by clot. On the other hand, the presence of pulsations may be deceiving, since there may be transmission of pulsations by a tail thrombus. Theoretically, this should produce a linear thrust (Nordentoft's sign) instead of the normal expansile type of pulsation, but this distinction may be difficult in the presence of much subcutaneous tissue. Tenderness at the site of embolus is not present early, but depends on the development of inflammatory changes in the intima. Pallor occurs early, and later, mottled cyanosis. "Marbled" blanching generally means complete arterial obstruction which will not respond to antispasmodic drugs or blocking of the sympathetic fibers. Late manifestations include motor or sensory paralysis as ischemia produces physiologic interruption of nerve and muscle function.

Differential diagnosis from thrombosis of the aorta is not difficult, since in the latter there is a gradual onset of symptoms related to the slow development of a reduction in peripheral circulation. However, in cases of thrombosis the circulation may become inadequate rather suddenly and the onset of pain and evidences of circulatory inadequacy may therefore appear to be an acute and recent process. The history will, however, differentiate this type of case from aortic embolism.

According to the author, embolectomy is the only life-saving treatment for a patient with an aortic embolus. He points out that almost invariably failure to restore the circulation results in death from gangrene. The general condition of the patient is the deciding factor as to whether to use the transabdominal approach or the indirect approach through the femoral vessels.

ABRAMSON.

Gomez, G. E.: Question of Cardiac Hypertrophy in Residents of High Altitudes.
J. A. M. A. 137:1297 (Aug. 7), 1948.

Gomez presents a statistical study of cardiac size of 638 residents of Bogota, Colombia, in an attempt to determine whether existence at the altitude of Bogota (8,016 feet above sea level) is associated with demonstrable cardiac enlargement. Two groups of subjects were studied. The first group, numbering 480, consisted of 182 medical students between the ages of 17 and 30 years, who had lived in Bogota for two or more years, and 298 normal persons of both sexes between the ages of 17 and 50, some of whom were natives of the city and others of whom were recent arrivals. The second group, numbering 158, was composed of seventy-seven soldiers with

a minimum service of six months in the army and a residence in Bogota of two years, and eighty-one soldiers with six months' service in places close to sea level who had come to Bogota only twelve days previously.

Teleroentgenograms in moderate inspiration were taken of each subject and the transverse-diameter of the cardiac silhouette was determined. The height and weight of each subject were measured.

Statistical analysis of the transverse diameters, correlated with the heights and weights of the nonmilitary group of 480 subjects, produced results identical with those which had previously been obtained by Ungerleider and Clark in a study of 1,460 normal persons living at altitudes close to sea level. The authors conclude, therefore, that residence at an altitude of 8,016 feet above sea level does not bring about demonstrable cardiac enlargement.

Similar analysis of the findings in the military group showed evidence of slight cardiac enlargement. Inasmuch as the values for those soldiers who had been in Bogota for some time were identical with those who had only recently arrived at the higher altitude, the authors believe that the slight increase in heart size in the military group is probably a result of the rigorous physical training to which the soldiers are subjected.

HANNO.

McGee, C. J., Priest, W. S., and Kenney, D.: Subacute Bacterial Endocarditis Due to *Hemophilus Parainfluenzae*. J. A. M. A. 137:1315 (Aug. 7), 1948.

An 8-year-old boy with rheumatic heart disease developed a subacute bacterial endocarditis complicated by a left hemiplegia, evidently embolic in nature. Early in the illness *Streptococcus viridans* had been reported in blood cultures and a course of sulfathiazole had been given over a period of six weeks without effect. Nine weeks after the onset of the illness, penicillin was administered in a dosage of 500,000 units daily by continuous intravenous drip, and repeated blood cultures showed the presence of *Hemophilus parainfluenzae*. The blood cultures remained positive with penicillin therapy, and in vitro studies showed that the organism was not inhibited by any concentration of penicillin, but was inhibited by a sulfonamide concentration of 3.0 mg. per cent. Penicillin therapy was continued and, in addition, sulfamerazine was administered in a dosage which maintained the blood level between 8.0 and 12.0 mg. per cent. The combined treatment was continued for fifty-two days, following which sulfamerazine alone was given for thirteen days. The blood culture became negative within twenty-four hours after the combined treatment was begun and remained negative on repeated determinations during the course of therapy and after treatment was discontinued. The patient recovered and has remained well during a two-year follow-up. The only residua of the hemiplegia are slight flexion contractures of the left thumb and index finger.

In attempting to explain why a combination of penicillin and a sulfonamide effected a cure when a sulfonamide alone did not, the authors advance the theory that penicillin, which has been shown to penetrate fibrin, somehow enabled the sulfonamide drug to penetrate the fibrin barrier of the valvular vegetations.

The case reported represents the first recovery of a patient with subacute bacterial endocarditis due to *H. parainfluenzae*. Each of the forty cases previously reported in the literature terminated in death.

HANNO.

Brozek, J., Chapman, C. B., and Keys, A.: Drastic Food Restriction: Effect on Cardiovascular Dynamics in Normotensive and Hypertensive Conditions. J. A. M. A. 137:1569 (Aug. 28), 1948.

The authors review the cardiovascular effects of drastic food restriction and recovery from semistarvation which were noted experimentally in a controlled study on normotensive subjects and which were observed in segments of the European population during World War II, as described in the recent European literature.

In the experimental study, thirty-four normal young men were placed on a restricted dietary intake of 1,600 calories and 49 grams of protein daily for a period of six months. No attempt at sodium limitation was made. The average body weight fell 23.9 per cent; the mean systolic blood pressure fell 11.1 per cent; the mean diastolic pressure fell 7.73 per cent; the mean pulse rate decreased to 37; the average basal metabolic rate decreased to minus 39.9 per cent; and a striking decrease in heart size was noted. At no time during the semistarvation period was circulatory failure observed, although edema appeared uniformly. Controlled rehabilitation in thirty-two subjects was instituted for a period of twelve weeks with a diet of 2,449 calories and 72.85 grams of protein per day. During this period the systolic and diastolic pressures rose slowly to levels slightly below the prestarvation readings. In a group of nineteen subjects, after thirty-three weeks of dietary rehabilitation, the average systolic and diastolic pressures were found to be slightly higher than the original levels, but in the seven subjects who were examined fifty-eight weeks after the end of the strict dietary limitation, the average blood pressure had returned to prestarvation values. In twelve of the men it was observed that a large increase in the caloric intake following the twelfth week of rehabilitation was associated with a rise of both the systolic and diastolic pressures to values slightly above the control values and a rise in the average venous blood pressure. Concomitantly, a moderate tachycardia and exertional dyspnea appeared. One subject, who began to consume from 7,000 to 10,000 calories a day following the twelve weeks of controlled rehabilitation, developed mild congestive failure which responded to dietary restriction, fluid limitation, the administration of ammonium chloride, and bed rest.

The experience of various European observers during the recent war years has shown that conditions of undernourishment, as pertained to prisoners of war, concentration camp inmates, and the general population of the war-devastated countries, brought about decreases in blood pressure and pulse rate in both normal and hypertensive subjects. During recovery from semistarvation, not only does the blood pressure return to normal levels but may also overshoot the mark to reach frankly hypertensive levels.

Of particular interest are the extensive observations made in Leningrad before the outbreak of the war, during the siege period of severe dietary limitation, and during the period following the partial lifting of the siege. During the period of reduced food intake, the incidence of hypertension decreased and in a large number of hypertensive patients reduction of blood pressure to normal or near normal levels occurred. There was, in addition, a definite decrease in the incidence and intensity of symptoms commonly associated with hypertension; angina pectoris and myocardial infarction were encountered less commonly than before the war. Following the end of the siege when the food supply became more plentiful, the incidence of hypertension reached epidemic proportions and the incidence of cardiac insufficiency in hypertensive patients increased. The impression was gained that in some hypertensive patients the disease became much more severe in the poststarvation period than it had been in the presiege period. Frank neuroretinitis and retinal hemorrhages and exudates were observed in a larger number of hypertensive patients than in the prestarvation period, but, interestingly, the incidence of associated renal changes decreased, while malignant nephrosclerosis virtually disappeared.

The results of the European experiences and of the authors' controlled study indicate quite definitely that drastic dietary restriction causes a fall in blood pressure in most normal persons and hypertensive patients. It would seem that the primary causative factor is the caloric limitation. Salt intake was not specifically limited in any of the groups observed, and even if some decrease in sodium intake were present, it was not comparable to the extremely low levels of the Kempner "rice-diet" regimen.

The authors conclude that a diet causing moderate weight reduction is therapeutically indicated in the management of hypertension and that a stringent program of the Kempner type may well be utilized in the treatment of the more severe cases. They warn, however, that in selecting cases for treatment by severe dietary limitation the risk of the patient's becoming worse than before, if he abandons the program, must be kept in mind.

Lampson, R. S., Schaeffer, W. C., and Lincoln, J. R.: **Acute Circulatory Arrest From Ventricular Fibrillation for Twenty-Seven Minutes With Complete Recovery.** J. A. M. A. 137:1575 (Aug. 28), 1948.

The authors report the case of a 7-year-old boy who developed sudden circulatory arrest following completion of operative repair of a deep laceration of the foot. The surgical procedure lasted about 75 minutes and was done under open drop ether with cyclopropane induction.

The patient's condition during the operation was good, but after the administration of the anesthesia had been discontinued, the pulse abruptly stopped, spontaneous respiration ceased, and ashen pallor became evident. No heart sounds could be heard on auscultation. Within two and one-half to three minutes following the onset of the circulatory arrest, an incision was made in the left fifth intercostal space directly into the left pleural cavity. The heart was soft to the palpating fingers of the surgeon, and visual observation showed the fine ripples of fibrillation in the left ventricular musculature. Rhythmic cardiac massage was immediately instituted by intermittent compression of the heart against the sternum at a rate of about 60 per minute, and pulsations were then noted at the wrist. At the same time, respiration was maintained by rhythmic compression of the breathing bag containing oxygen. The patient's general appearance began to improve. Fifteen minutes later, when the heart still was not beating spontaneously, 3.0 c.c. of a 1 per cent solution of procaine hydrochloride was given intravenously, and blood transfusion was started. At about this time spontaneous respirations returned. A second dose of 2.0 c.c. of 1 per cent procaine hydrochloride was administered by vein about twenty-six and one-half minutes after the onset of the circulatory arrest, and some thirty seconds later the heart began to stiffen and irregular spontaneous contractions set in. Two minutes later a normal rhythm with strong pulsations supervened.

An electrocardiographic tracing begun before spontaneous contractions of the heart had set in revealed the characteristic findings of ventricular fibrillation, the bizarre ventricular complexes occurring at a rate of about 365 per minute. This was followed by a short period where no evidence of cardiac activity was present, following which a run of ten aberrant arrhythmic ventricular contractions, some preceded by P waves, occurred. A normal sinus rhythm supervened, the QRS complexes being bizarre and of small amplitude and the S-T interval somewhat depressed for a few seconds. The chest wound was closed after penicillin and procaine hydrochloride had been flushed over the pericardium, and the patient was placed in an oxygen tent. Convalescence was complicated by evidences of temporary cerebral dysfunction as a result of the cerebral anoxia, but gradual and complete recovery took place, and the patient was discharged on the twenty-sixth postoperative day. Several electrocardiograms taken during convalescence were within normal limits.

The authors emphasize that the proper measures must be promptly taken when acute circulatory arrest sets in if certain death is to be averted. Because of the rapid development of cerebral anoxemia, complete recovery is not to be expected unless the circulatory arrest has been corrected within three minutes, and survival is unlikely if the elapsed time is more than eight minutes. They point out that the catastrophe is most likely to occur during light anesthesia, in either the induction or recovery phases, when the myocardium is hyperirritable, and that circulatory arrest may be due to either cardiac standstill or ventricular fibrillation. In either case, the circulation must be promptly restored by direct rhythmic cardiac massage and respiration must be artificially maintained with high concentrations of oxygen. Further treatment is then dictated by the type of cardiac disorder present. If ventricular fibrillation is the cause of the circulatory arrest, as evidenced by the direct observation of fibrillatory ripples or by the characteristic electrocardiographic findings, 5.0 to 10 c.c. of a 1 per cent solution of procaine hydrochloride should be administered intravenously or directly into the heart to reduce myocardial irritability. If defibrillation does not occur, the dose may be repeated or electrical stimulation, as used by Beck, can be resorted to if the equipment is available. Epinephrine hydrochloride is contraindicated in the presence of ventricular fibrillation because it makes an irritable myocardium even more irritable. Following the restoration of a normal rhythm, however, epinephrine may be of value in strengthening the contraction of the heart. If the cause of the circulatory arrest is cardiac standstill, as shown by a visibly quiet heart or by the absence of any evidence of activity

electrocardiographically, epinephrine, in a dose not exceeding 1.0 c.c. of a 1:1,000 dilution, may be administered intravenously, into the myocardium, or directly into the heart. An excess of epinephrine may throw a heart in standstill into ventricular fibrillation. If shock and hemorrhage are present, transfusion is indicated in order to insure adequate cardiac filling.

HANNO.

Cohen, H., and Harrison, C. V.: Temporal Arteritis: A Report of Three Cases. J. Clin. Path. 1:212 (Aug.), 1948.

The cases reported in this paper were all of men, though in previously recorded cases there have been slightly more women than men. The duration of the disease in these three cases was fifteen, eight, and twenty-three weeks, which is shorter than average.

In this series Case 1 recovered completely. Case 3 also recovered, but was left with blindness in his left eye. Case 2 died from myocardial infarction six months after discharge. In Case 1 the lesion appeared to be limited to the temporal arteries, in Case 2 the right circumflex artery was involved, and in Case 3 there was blindness in the left eye due to thrombosis of the central retinal artery.

That the disease is not a localized process is suggested by the frequent occurrence of pyrexia and pains in body and limbs and by a degree of systemic illness out of proportion to the physical findings. The outstanding symptom in all three cases, and in all recorded cases, has been pain in the head, which is usually resistant to analgesics. Removal of a segment of the affected temporal artery for biopsy was certainly of value in relieving symptoms in these cases. It has been suggested that this is due to the interruption of the accompanying nerves.

Nothing is known of the etiology of the disease, and though many of the clinical features suggest an infective cause, so far all attempts to isolate an organism have been fruitless. Nevertheless, the disease presents a uniform pattern which differentiates it from polyarteritis nodosa or Buerger's disease.

BELLET

Frankland, A. W.: Embolism After Penicillin-Oil-Beeswax. J. Clin. Path. 1:244, (Aug.), 1948.

The author was able to find only one previously published account of oil embolism following the use of penicillin in an oil-wax medium. In the case described in this report, a mild immediate reaction occurred after an injection of penicillin in oil-wax; the reaction was apparently due to oil embolism.

A 30-year-old woman with ulcerative colitis was given an injection of 600,000 units in 2.0 ml. of calcium penicillin suspended in peanut oil with 4.8 per cent beeswax. The nurse who gave the injection was not sure that the usual precautions of making sure the needle was not in a vein had been carried out. Immediately after the injection the patient felt quite faint; however, five minutes later she said she was feeling quite well. A specimen of sputum was collected the following day. No precautions were taken to make sure that this was not contaminated with any oil or fat from a food source. A further specimen of sputum was taken three days later; however, only in the specimen taken the first day after the penicillin injection and only in certain parts of the field could many oil globules be seen; all these were extracellular and most of them were very minute. Examination of a slide containing stained sputum, and also slides containing unstained and stained penicillin in oil-wax, showed that in no case was there rotation of the plane of polarized light. It is suggested, therefore, that the oil in the sputum had as its source the penicillin oil-wax injection given into the buttock.

BELLET.

Smull, K., Wissler, R. W., and Watson, J. M.: The Effect of Sodium Salicylate Upon Serum Disease in Rabbits. J. Lab. & Clin. Med. 33:936 (Aug.), 1948.

Using rabbits, the authors tested the influence of sodium salicylate therapy upon the lesions resulting from the injection of large intravenous doses of normal horse serum. Twelve rabbits received two intravenous injections of sterile normal horse serum fifteen to sixteen days apart,

while twelve similarly treated rabbits received large doses of sodium salicylate starting six days after the first injection of horse serum. The drug was administered in quantities designed to maintain an average of about 250 gamma per milliliter throughout each twenty-four hour period. Sedimentation rates and blood salicylate levels were followed.

Normal sedimentation rates persisted in the salicylate-treated animals which did not receive intravenous horse serum. Most of the animals given horse serum showed an increase in the rate above 20 mm. after the first or second injection. Salicylate therapy did not exert any notable effect on the sedimentation rate in spite of the fact that the lesions were less severe in this group of animals. Sustained hypertension was not noted in any of the animals, even in those which developed marked generalized arteritis. In the salicylate-treated animals it was found that levels of 350 gamma per milliliter could not be maintained without producing intoxication and death.

Despite the small series, the results suggest that salicylate treatment had depressed the developing arteritis in the treated group. In the salicylate-treated rabbits the authors found a moderate depression in the concentration of circulating antibody to horse serum which occurred eighteen to twenty-two days after the first injection of horse serum.

Microscopically, the arteritis, when present, usually was seen in the myocardium, lungs, pancreas, mesentery, stomach, kidneys, liver, adrenals, diaphragm, and testes or uterus. Most of the valvular changes were proliferative in type and were found predominantly at the base of the valve leaflets and were confined almost entirely to the mitral and aortic valves as they are in rheumatic fever.

The authors stress that at present one must be cautious in assuming that the inhibitory effect of salicylates upon the lesions of rabbit serum disease can be applied to the lesions of rheumatic fever.

KLINE.

Green, R. S., Iglaue, A., and McGuire, J.: Alterations of Radial or Brachial Intra-Arterial Blood Pressure and of the Electrocardiogram Induced by Tilting. J. Lab. & Clin. Med. 33:951 (Aug.), 1948.

In this study careful analysis has been made of the response of heart rate and blood pressure to tilting in normal subjects in order to establish a standard to evaluate changed reactions due to disease or drugs. This report details the findings in fifteen healthy young adults considered to have normal cardiovascular systems. The subjects were tilted at a moderate rate from the 20° head-up position to the 45° head-down position. This position was maintained for at least fifteen seconds and at least three sets of observations were made on each subject.

Elevation of arterial blood pressure in the arm occurred during the head-down tilt in all of the subjects studied. The average rise was 19 mm. Hg systolic and 16 mm. Hg diastolic. This was followed by a gradual fall lasting from eight to eighteen seconds until the blood pressure reached a level that was usually slightly higher than that obtained in the erect position. During the return to the head-up position, the blood pressure fell in all of the subjects, the fall averaging 14 mm. systolic and 13 mm. diastolic. The blood pressure returned to the starting level within eight to eighteen seconds of the completion of the tilt. Assumption of the head-down tilt position invariably caused slowing of the heart rate. With the head-up tilt position the heart rate suddenly increased following the drop in blood pressure. This resulted in a rate that was more rapid than the initial rate in this position in about one-half of the subjects.

The authors found that following the assumption of the 45° head-down position there resulted a slowing of the heart rate determined from prolongation of the P-R interval and in 20 per cent of normal subjects the P wave gradually decreased in size and finally disappeared for several beats. The disappearance of the P wave was not preceded by a shortening of the P-R interval. This change did not invariably occur in the same individual on successive tilting.

KLINE.

LeRoy, G. V., and Nalefsi, L. A.: Dicumarol in Experimental Myocardial Infarction. J. Lab. & Clin. Med. 33:961 (Aug.), 1948.

The present study was undertaken to investigate the influence of Dicumarol therapy on the healing of experimental myocardial infarcts. Attention was directed particularly to: (1) the mortality rate after the administration of Dicumarol, (2) the extent and character of the infarct, grossly and microscopically, (3) the evolution of the electrocardiographic changes, and (4) the behavior of the sedimentation rate. The infarcts were produced by ligation of the anterior descending branch of the left coronary artery. Serial determinations of the prothrombin time, the hematocrit, the sedimentation rate, and serial electrocardiograms were made on all dogs. The animals were sacrificed at intervals of five to twenty-two days after the ligation of the coronary artery.

Seven of the thirty-two dogs died within twenty-four hours after the production of coronary occlusion, giving an immediate mortality of 21.8 per cent. Five of the dogs treated with Dicumarol developed complications as a result of the abnormal hemorrhagic tendency that resulted. There was no mural thrombosis in any animal, and there was no evidence that any thromboembolic phenomena occurred. Serial electrocardiograms did not show any consistent significant difference between the treated animals and the control animals. There did not appear to be any significant, consistent difference in the size of the infarcts or the amount of hemorrhagic infiltration in the two groups of animals. Microscopic examination of representative sections revealed no obvious difference between the healing infarctions in the treated animals and in the control animals. The variations in the sedimentation rate were not consistent and were of no importance in evaluating the course of experimental myocardial infarction.

The authors conclude that Dicumarol did not have any demonstrable deleterious influence on the healing of experimental myocardial infarction in dogs.

KLINE.

Balkin, S. S., and Gootnick, A.: The Effects of Dicumarol on the Electrocardiogram. J. Lab. & Clin. Med. 33:972 (Aug.), 1948.

Dicumarol was given to forty-eight subjects. Of these, twelve were normal and sixteen had various types of cardiovascular disease with abnormal electrocardiographic patterns which remained stable during preliminary observation. In addition, fourteen patients with acute myocardial infarction who were on a Dicumarol regimen were studied. A separate group of six digitalized patients whose electrocardiograms had remained stable under prolonged observation were also treated with Dicumarol to observe the possible modifying influence of the drug on the several degrees of digitalis effect. Serial electrocardiograms, composed of Leads I, II, III, CF₁, CF₂, and CF₃, were taken in all subjects and were analyzed with respect to rhythm, auriculoventricular and intraventricular conduction, Q-T duration, RS-T level, and the amplitude of auricular and ventricular components. Dicumarol was given until the prothrombin level remained between 15 and 25 per cent of normal.

No significant electrocardiographic deviations attributable to Dicumarol were observed in any of the subjects.

KLINE.

Hauptmann, A., and Myerson, A.: Studies of Finger Capillaries in Schizophrenia and Manic-Depressive Psychoses. J. Nerv. & Ment. Dis. 108:91 (Aug.), 1948.

The authors examined seventy-five individuals diagnosed as schizophrenics and subdivided as follows: forty-nine undoubted schizophrenics, ten schizophrenics with predominant paranoid symptoms, four schizophrenics with outstanding hallucinations, and twelve questionable schizophrenics. They examined thirty-seven patients in the manic-depressive group (thirty-two in a depressive state and five in a manic state) and three patients with other forms of psychoses. The total was 115 cases.

The mentally and emotionally "normal" individuals showed a normal structure of the capillaries of the fingernail fold. Mentally deficient children, whose retardation was not caused by

environmental factors, showed an immature, arrested picture of their finger capillaries. The capillary picture of the schizophrenics was quite different from that of the patients with manic-depressive manifestations. The main feature of the schizophrenics was an immature formation of the capillaries, whereas manic-depressives showed twisted capillaries.

The capillary picture of the schizophrenics was present in children prior to the end stage of the capillary development. The most pronounced immature pictures were found in those schizophrenics who showed all the classical clinical features of this disease. The rapidity of the development of the psychosis and its chronicity were not related to the capillary picture. Of the forty-nine undoubted schizophrenics, thirty-five (71.5 per cent) showed this typical immature picture. The capillary picture of the remaining fourteen patients was often partially immature; moreover, the clinical picture permitted some doubt in the diagnosis. These fourteen patients with schizophrenia with a nontypical, immature capillary picture stand very close to the group of twelve doubtful schizophrenics in respect to the capillary picture. The abnormal capillary picture in schizophrenics did not change during the course of the disease regardless of remission, new attacks, or electric shock treatments.

The capillary picture of the depressive or of the manic patients was markedly different from that of the schizophrenics. It was characterized by twisted capillaries. This capillary picture is the picture found in constitutional psychoneurotics. Of the thirty-two patients with depressive manifestations, twenty-four (75 per cent) showed this picture; of thirty-six patients with manic manifestations twenty-eight (78 per cent) had this characteristic capillary pattern.

In some cases the capillary picture corresponded better to the course of the psychosis than the clinical diagnosis made at the beginning of the illness. The clinical features of immaturity in schizophrenia find their bodily correlation in the immature capillary picture.

BELLET.

Mowbray, R., and Bowley, C. C.: Congenital Complete Heart Block Complicating Pregnancy. J. Obst. & Gynaec. Brit. Emp. 55:438 (Aug.), 1948.

Three cases of congenital heart block complicating pregnancy are described and discussed. The authors point out that the most frequent associated anatomic defect is a patent interventricular septum, but heart block has also been described with pulmonary stenosis, aorto-pulmonary patency, dextrocardia, atrial septal defect, and other congenital abnormalities. In this condition the prognosis is usually good.

The authors were unable to find a case reported where congenital heart block and atrial septal defect complicated pregnancy, as in their first case. The second case was only diagnosed late in pregnancy after the bradycardia had been noticed in a prenatal clinic. It seemed probable that an interventricular defect was the associated anatomic abnormality in this case. The third patient was already known to be suffering from congenital heart block, but on the data available, it was impossible to state what the underlying anatomic condition was. The first two patients showed ventricular rates over 40 per minute, while the rate in the third patient varied from 32 to 72 beats per minute.

The third case illustrated the possible effect of a complicating toxemia of pregnancy with hypertension on an already abnormal heart. There seemed little doubt that in this case the cardiac failure from which the patient died was precipitated, not primarily by the pregnancy, but by the toxemia and hypertension. The second patient also showed a mild degree of toxemia in both her pregnancies which was insufficient in degree to affect the cardiac state adversely.

BELLET.

Williams, F., and Leonards, J. R.: The Effect of Sodium Bicarbonate on the Renal Excretion of Salicylate. J. Pharmacol. & Exper. Therap. 93:401 (Aug.), 1948.

The authors demonstrated that bicarbonate had no effect on intestinal absorption of salicylates. However, in both the dog and man the renal excretion of salicylate was markedly increased by the administration of bicarbonate. This effect was more marked in the dog, as less of the salicylate was bound to the serum proteins and more passed through the glomerular filter. Bicarbonate

had no effect upon the binding of salicylate by the plasma proteins in either dog or man. The increase in excretion was due to an increased clearance value. In man the salicylate clearance was approximately equal to the urea clearance and with bicarbonate administration the salicylate clearance exceeded that of urea and actually approached the glomerular filtration rate.

The dose of bicarbonate used in man (5.0 to 7.0 Gm.) was in excess of the commonly used amounts in clinical medicine; furthermore, there were no prolonged determinations of salicylate blood levels with and without bicarbonate administration. However, the findings seemed to warrant further clinical evaluation.

GODFREY.

Short, D. W.: Occupational Aneurysm of the Palmar Arch. Lancet 255:217 (Aug. 7), 1948.

Traumatic true aneurysms in the palm, due to repeated minor injuries, are very uncommon, approximately eleven cases having been reported. Most aneurysms of this type are associated with the ulnar artery and are found deep in the inner border of the hypothenar eminence. In the author's single case, the patient, a marine engineer, sought medical advice because of a tender lump in the right palm. As part of his daily duties, he shifted a stiff reversing lever by hammering it with the palm of his hand. After two months of this type of work, he noted increasing tenderness over the area and a slowly growing swelling. The tumor was not mobile or pulsatile and felt like a cyst. On operation it was found to be a saccular aneurysm arising from the superficial palmar arch immediately distal to the deep branch of the ulnar artery.

Generally, the symptom in this condition is a persistent bruised feeling, with a tender swelling appearing later. Sensory disturbances are sometimes prominent.

ABRAMSON.

Mathews, F. P.: Enterococcal Endocarditis. Northwest Med. 47:581 (Aug.), 1948.

A 53-year-old mill worker was admitted to the hospital complaining of sore tongue, sore throat, and fever. A diagnosis of Ludwig's angina and rheumatic aortic stenosis was made. He had had rheumatic fever at 14 years of age and this had left him with a heart murmur. Ten days after admission the patient suddenly experienced severe substernal pain and the aortic murmur was found to have increased in intensity. The organism found in blood cultures was classified, on the basis of heat resistance, as an enterococcus, rather than as *Streptococcus viridans*.

A penicillin sensitivity test was performed on a subculture from the first blood culture. After forty-eight hours of incubation, growth was found to have been inhibited in the first two tubes but took place in three tubes of higher dilution. Accordingly, the penicillin dose, which had been begun at 20,000 units every four hours intravenously, was increased to 40,000 units every three hours. Two days later, following confirmation by the second blood culture, the dose was raised to 80,000 units every three hours. The neck symptoms cleared up and temperature gradually came down. Five weeks after admission the patient was discharged; at this time the only murmur present was the aortic systolic murmur which was present on admission. About one week later the patient was readmitted with marked dyspnea and return of substernal pain. The heart had apparently dilated further. The patient was digitalized and an oxygen tent applied, but signs of bronchospasm developed, and three days later the lungs became edematous and the patient died.

Necropsy revealed the immediate apparent cause of death to be an oval perforation through the posterior mitral valve leaflet, which was assumed to have taken place about a week before death, as its edges were partially healed.

The author points out that in this case of enterococcal endocarditis, the organism was sensitive to the bacteriostatic action of penicillin clinically and in vitro; because of the rupture of a mitral valve leaflet after the activity of the infectious process had apparently subsided, the case ended fatally.

BELLET.

Gover, M.: Variation of Blood Pressure and Heart Disease With Age, and the Correlation of Blood Pressure With Height and Weight. Pub. Health Rep. 63:34 (Aug. 20), 1948.

This survey by the Farm Security Administration is the only large-scale study of an exclusively low-income rural group.

When the percentage of the population with hypertension is computed, comparative studies often use different standards. But regardless of the criteria of hypertension, allowance for the "normal increase in mean blood pressure with advanced age" is rarely made. The author notes that the percentage of persons with high blood pressure does not increase as rapidly with age as it does when computed from a base which is not age-specific.

The chief finding of the author is that age-specific mean systolic blood pressure for members of low-income farm families is higher than in recorded observations for other population groups, mainly urban; mean diastolic blood pressure for the farm group does not differ greatly from that recorded for urban groups.

Low-income rural men under 30 years of age had a relatively high prevalence of heart disease; in men over 30 the rural rates are similar to those of urban industrial workers. The systolic pressure had a small but significant correlation with weight.

WAIFE.

Macht, D. I.: Penicillin, Streptomycin, Dicumarol and Blood Coagulation; Thromboplastic Properties of Penicillin Antibiotics. South. M. J. 41:720 (Aug.), 1948.

Experiments were made by the author using rabbits, cats, and dogs with injections of penicillin in various doses both intravenously and intramuscularly. He found that in all of the experiments such injections exerted thromboplastic effects. He studied the effect separately of the active principles of penicillin G, X, F, and K. He found that penicillin X was the most thromboplastic and that penicillin K was next in thromboplastic effectiveness. In experiments on rabbits and cats the author also found that the coagulation time was definitely shortened by streptomycin. The clot-promoting property of penicillin can be antagonized by the cautious administration of Dicumarol. He also found that in animals receiving large doses of Dicumarol which developed an extremely prolonged prothrombin and coagulation time with resultant hemorrhagic tendencies, the danger of hemorrhage can be effectively controlled by injections of penicillin.

The author concludes that clinically one must always be on guard against the added risk of thromboembolic accidents when administering antibiotics, especially in bacterial endocarditis where massive doses are used, and that heparin or Dicumarol should be administered in such cases. It was also found that x-ray increases the thromboplastic properties of penicillin.

KLINE.

Robb, J. S., Kaylor, C. T., and Turman, W. G.: A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart. Am. J. Med. 5:324 (Sept.), 1948.

In this investigation four human fetal hearts were used. The fetuses from which the hearts were obtained were of 15½, 20, 21, and 32 weeks' gestation, respectively. In three of these hearts the S-A node was found to extend almost around the entire entrance of the superior vena cava into the right auricle. Pathways, uninterrupted by connective tissue, made connections from this node to the A-V node. One of these extended from the posterior portion of the S-A node in the sulcus terminalis, then along the posterior atrial wall, thence horizontally along the A-V junctional area to the A-V node. Another extended from the anterior portion of the S-A node, anterior to the foramen ovale, to the upper, somewhat posterior portion of the A-V node. Still other strands from the S-A node connected through the right and left portions of the interatrial septum to the more distal portions of the A-V node and proximal portions of the bundle. None of these pathways was composed exclusively of specialized tissue. On the contrary, specialized cells appeared near the nodes but then spread out to make end-to-end transitions into ordinary atrial muscle. The silver preparations of one heart indicated that there was a con-

siderable supply of nerve fibers to the S-A node and also to the A-V node, but because of the lack of a differential stain for sympathetic fibers, no observations were made on their course or terminations. From the A-V node compact bundles of specialized cells streamed distally forming the bundle of His, which divides into two main outflows at the top of the interventricular septum. The authors confirmed the previous observation that the left outflow appears as a broad, flat sheet which eventually separates into anterior, posterior, and septal portions. However, they report that the right outflow does not consist of one single limb, although it is usually in discrete bands and not "sheet-like," as on the left. Connections from the main bundle and from all parts of the right and left branches to septal muscle were seen in all of the hearts.

In general, the cells throughout the specialized system are alike and are different from either auricular or ventricular cells. It was found that the nodes are imbedded in connective tissue which is well differentiated with the Masson and Mallory stains. The bundle, its branches, and the Purkinje transitions into ordinary heart muscle are all enclosed in a connective tissue sheath. Nothing was found that could be considered to be an end organ. Whenever a Purkinje strand was followed peripherally it eventually underwent gradual transition into an ordinary heart muscle fiber. This transition was always arranged end-to-end. The authors did not find an accessory bundle of His although multiple A-V bridges of ordinary muscle tissue were observed.

KLINE.

Littmann, D.: Abnormal Electrocardiograms in the Absence of Demonstrable Heart Disease. Am. J. Med. 5:337 (Sept.), 1948.

This author reports nine cases which illustrate the occurrence of inverted T waves in precordial leads in individuals without demonstrable heart disease. They were selected from 5,000 electrocardiograms which were read over a period of eighteen months. With one exception, none of the patients had any complaints referable to the heart. In that one case the symptoms were considered to be due to a marked cardiac neurosis and aerophagia.

The electrocardiogram of the first case revealed the presence of alternating ventricular premature beats. In Lead IVF the T wave of the sinus beat was sharply inverted. After several days of rest fewer extrasystoles were noted. The electrocardiogram at this time showed T-wave inversion only in the beat which followed the extrasystole.

The second and third cases showed inverted T waves in Leads CF₂ and CF₃ in one case and inverted T waves in all of the CF leads in the other. In both cases, however, the T waves in CR leads were upright and of normal amplitude. These two cases were considered to represent persistence of the juvenile pattern in the electrocardiogram of adults.

The next four cases were grouped together because of several common features. The limb leads contained T-wave deviations which varied from lowering and flattening to frank inversion. The most marked abnormalities, however, were noted in the precordial leads. The greatest degree of T-wave inversion occurred in leads made at or near the apex. In all of these subjects essentially normal curves were obtained with the passage of time or following vigorous exercise. The author suggests that these patients represent instances of normal hearts with unstable T waves.

In the eighth case the electrocardiogram showed T-wave inversions in Leads CF₂, CF₃, and CF₄ and in CR₂ and CR₃. It later became apparent that the curves obtained in the morning before the patient had eaten were normal, while those made later in the day were abnormal. No significant changes were observed following exercise, hyperventilation, or the administration of atropine or prostigmine.

In the ninth case the inversion of the T waves in the CF leads was due to a proved mediastinal emphysema and pneumothorax.

The author stresses that the electrocardiogram should be regarded merely as one diagnostic procedure which is to be integrated with other findings.

KLINE.

Taran, L. M., and Szilagyi, N.: Oxygen Therapy in Acute Rheumatic Carditis in Children. *Am. J. Med.* 5:379 (Sept.), 1948.

Forty-four children, 7 to 16 years of age, presenting unequivocal evidence of acute rheumatic carditis, were treated in oxygen chambers for an average period of twelve weeks. Temperature was kept constant at a level of 66° to 68°F. and the humidity fluctuated between 60 and 70 per cent. Carbon dioxide concentration was permitted to rise to a level of 1.3 to 1.5 per cent. Other forms of cardiac therapy were instituted only when urgently indicated.

Twenty-four of the forty-four patients showed definite clinical improvement as a result of oxygen therapy as manifested by a marked and rapid drop in the heart rate and a decrease in respiratory rate. Precordial pain and evidence of cardiac fatigue subsided. In some instances there was an increase in diuresis and a significant drop in the previously elevated venous pressure. The tumultuous character of the heart action was changed to a quiet and slow rhythm. In addition, the clinical behavior of the patient was profoundly changed in favor of a more complete recovery. It was also noted that in the greater majority of the "responsive" patients there was an increase in appetite and weight along with improvement in facial coloring.

Seventeen of the forty-four treated children were not benefited by oxygen therapy. Most of these were advanced cardiacs with a long-standing carditis and evidence of minimal or severe heart failure. Three children could not tolerate oxygen therapy. They belonged to the "bronchitic" type of rheumatic carditis.

The authors observed that oxygen therapy did not alter the established anatomic cardiac damage but reduced significantly the cardiac functional disability which is present during the acute phase of the disease.

KLINE.

Taran, L. M., and Szilagyi, N.: Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children With Acute Rheumatic Carditis. *Am. J. Med.* 5:392 (Sept.), 1948.

This paper reports the relationship of systole to diastole in children with acute carditis receiving oxygen therapy.

Fifteen girls, 10 to 14 years of age, were chosen for this study. All had unequivocal histories of rheumatic fever and during the period of observation had obvious clinical signs and symptoms of rheumatic carditis. All patients presented moderate to marked prolongation of the electrical systole (Q-T interval). During the entire period of observation no medication was given except an occasional sedative. None received digitalis for more than three weeks preceding the period of observation. After a control period of not less than two weeks these patients were introduced into an oxygen chamber where the oxygen concentration was 45 to 50 per cent and the carbon dioxide concentration level fluctuated between 1 and 1.3 per cent.

In all of the cases studied the cardiac rate was decreased and there was a rapid return to a more normal relationship of systole to diastole when oxygen therapy was begun. This was attained not by a significant shortening of the systolic period (Q-T) but rather by a marked lengthening of the diastolic period (T-Q). This occurred in all cases irrespective of the time it took to effect the result after oxygen therapy was instituted. All patients showed unequivocal clinical improvement as the electrical sequence of events approached a more normal relationship.

KLINE.

De Palma, A. F.: Scalenus Anticus Syndrome Treated by Surgery and Skeletal Trac-tion. *Am. J. Surg.* 76:274 (Sept.), 1948.

The scalenus anticus syndrome is characterized by neurological and circulatory findings. The neurological findings consist of sensory symptoms in the form of paresthesia and pain along the flexor and ulnar surfaces of the forearm, shoulder, angle of the scapula, pectoral muscles, and often in the root of the neck and ear of the affected side. Later there may be muscular atrophy of the thenar eminence or of the interossei muscles.

The circulatory manifestations consist of decreased cutaneous temperature, numbness, and formication in the extremity and frequently cyanosis and puffiness of the hand and forearm and diminution of the radial pulse. Later trophic changes, to the point of gangrene of the finger tips, may intervene. Obliteration of the radial pulse can be produced by downward traction on the involved extremity or when the patient extends the cervical spine and rotates the head toward the affected side while taking a deep breath. A very common finding is tenderness in the supraclavicular fossa, especially over the distal third of the scalenus anticus muscle, lateral to the sternocleidomastoid muscle. The scalenus anticus muscle may be tense, contracted, and even hypertrophied.

The basis for these findings is a disturbance involving the brachial plexus and the subclavian vessels of the affected extremity. The nervous manifestations are the result of irritation of the brachial plexus, especially of its middle and lower trunks, causing spasm and contraction of the scalenus anticus muscle, which, in turn, results in an elevation of the first rib. As a consequence, greater stimulation of the plexus occurs, with perpetuation of the spasm of the muscle.

The cause of the vascular manifestations is not clear. They may be the result of stimulation of the sympathetic fibers in the lowest nerve trunk or of direct pressure on the brachial plexus and subclavian artery.

The predisposing factors which contribute to the initiation of the scalenus anticus syndrome may be the presence of a cervical rib, congenital anomalies of the cervical vertebrae and of the scalenus anticus muscle, and a postfixed brachial plexus. Among the exciting factors are the descent of the shoulders beyond normal limits in adulthood, pressure of the scalenus anticus muscle on the plexus during the period of greatest activity and muscular development, and poor posture involving an abnormal droop of the shoulder girdles.

The author believes that in the milder form of this syndrome conservative measures should be used in treatment. In the presence of poor posture, corrective exercises and some type of support to pull the shoulder girdle upward and backward will give considerable and prompt relief. When the syndrome is the result of direct or indirect trauma to the scalenus anticus muscle, rest to the part with the arm in an elevated position will also alleviate the symptoms. Repeated procaine injections into the muscle are worth while as an adjunct therapy.

When conservative measures fail, traction on the cervical spine or division of the scalenus anticus muscle may have to be performed. Traction is obtained by means of steel hooks inserted subperiosteally beneath the zygoma. Straight traction is made on the cervical spine by means of a 5- to 10-pound weight. Symptoms usually disappear within six to eight hours after traction has been applied, but this is maintained for ten days, after which the patient is made to wear a light cervical collar for two weeks. Of the author's sixteen patients treated by traction, all were relieved of pain, except one who had a recurrence of symptoms.

ABRAMSON.

Bageant, W. E., and Rapee, L. A.: The Treatment of Pulmonary Embolus by Stellate Block. *Anesthesiology* 8:500 (Sept.), 1947.

The authors present two cases in which a stellate block was done for episodes of severe pulmonary embolism, with dramatic and immediate relief of chest pain, dyspnea, orthopnea, and cyanosis, and with a probable reversal of a shock syndrome.

A 36-year-old man was admitted to the hospital because of a severe grade of heart failure. He manifested shortness of breath and swelling of the feet and ankles. On the second hospital day auricular fibrillation developed. On the eighth hospital day quinidine was given for the fibrillation. The cardiac rhythm became regular, but on the fourteenth hospital day, the patient complained of a sudden onset of severe pain in the right lower chest. He had associated dyspnea, orthopnea, cyanosis, an elevation of temperature, marked apprehension, moderate sweating, and he expectorated a small amount of blood-tinged sputum. Later, a severe pain developed over the left chest as well. A stellate block was done on the right side with 2.5 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. Within a few minutes the patient experienced almost complete relief of pain in the right chest and later also in the left chest. His breathing became easier, his chest

expansion greater, chest splinting was less, and he fell asleep for the first time since the onset of the pulmonary infarction. A roentgenogram confirmed the diagnosis of pulmonary infarction of the right chest. The patient remained comfortable until the twenty-second hospital day, when he had a second pulmonary embolus. A second stellate block was done immediately on the right side with 6.0 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. He experienced almost immediate relief of his pain and dyspnea. The patient remained comfortable until the thirty-first hospital day, at which time he had his third pulmonary embolus. A stellate block was not done at this time, for he was semicomatose and he remained so until his death. Necropsy revealed rheumatic myocarditis with aortic stenosis and insufficiency, cardiac failure, multiple pulmonary infarcts of the right lung, and old multiple infarcts of the left lung.

The second case was that of a 39-year-old woman who was suddenly awakened with a severe, excruciating pain in the right chest. She was admitted to the hospital the same day. A roentgenogram confirmed the clinical diagnosis of pulmonary embolism. A stellate block was done with 3.0 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. After an interval of five minutes, the patient experienced marked relief of chest pain and was immediately able to breathe more freely and deeply. On the afternoon of this same date, under spinal anesthesia, the femoral veins were ligated, since these veins were considered to be the source of the embolus.

The authors state that blocking of the stellate ganglion interrupts the painful irritative impulses arising from the sympathetic nerves innervating the pulmonary vessels. This apparently breaks up the vicious cycle (pulmonary and/or coronary vascular spasm phenomena) by blocking the painful nerve impulses as stated and permitting vasodilatation of the pulmonary vessels. There is immediate relief of pain, dyspnea, orthopnea, and cyanosis; a greater chest expansion results and the state of shock is apparently reversed.

BELLET.

Blackman, N. S., and Hamilton, C. I., Jr.: Serial Electrocardiographic Changes in Young Adults With Acute Rheumatic Fever; Report of 62 Cases. *Ann. Int. Med.* 29:416 (Sept.), 1948.

Sixty-two young white men, who had been admitted to the hospital with an initial episode of subacute or acute arthritis involving one or more joints, were studied with serial electrocardiograms in which only the three standard limb leads were used. In all members of this group, initial treatment consisted of bed rest and the administration 5 to 15 Gm. of sodium salicylate daily. Electrocardiograms were obtained every other day from the first week of hospitalization and twice each week thereafter.

Slightly over 40 per cent showed transitory prolongation of the P-R interval. In all instances prolongation of the P-R interval returned to normal before discharge. A transitory Wenckebach phenomenon was seen in one case. No instances of complete A-V heart block were recorded. The Q-T interval was found to be prolonged in 35 per cent of the cases. In four of this number, it was the only demonstrable deviation from normal in the electrocardiogram. Two instances of wandering pacemaker were recorded. In addition, other disturbances of rhythm, such as auricular premature contractions, ventricular premature contractions, nodal rhythm, sinus bradycardia, and paroxysmal tachycardia, were occasionally observed.

Changes in the RS-T segment were chiefly confined to fluctuation in the elevation and depression of these segments and occurred in 22.5 per cent of the cases. Transient variations of the T wave were the most common abnormality noted. At one end of the scale were those cases with increased amplitude of the T wave and at the other end, those cases with deep inversion of the T wave. Between these two extremes were intermediate variations of this deflection. All of the 98.4 per cent of cases showing abnormalities in the serial records showed these changes within the first two weeks of the onset of the clinical symptoms. The implications of this last observation are discussed by the authors.

Emphasis is placed upon the fact that early in the course of the illness the diagnosis of rheumatic carditis frequently must depend upon changing electrocardiographic patterns in serial records.

WENDKOS.

Jones, H. E., and Marshall, A. G.: Isolated (Fiedler's) Myocarditis. *Arch. Dis. Childhood* 23:201 (Sept.), 1948.

A fatal case of idiopathic (Fiedler's) myocarditis is described in a male infant who experienced no illness until 9 months of age, when he became fretful and refused food. For the subsequent weeks until death at 11 months he was pale, listless, and vomited on most days. He was never febrile. Two days following onset of symptoms he was given sulfonamide (amount unknown) for five days. Five weeks after onset he was hospitalized. The chief findings were slight cyanosis and cardiac and liver enlargement. He developed periodic attacks of dyspnea and died in a severe episode of dyspnea.

The main findings at autopsy were general dilatation of auricles and ventricles with a thickening of their walls and gross thickening of the endocardium of the left auricle. No valvular lesions were observed. Sections from auricles and ventricles, mitral valve, and papillary muscle all showed a diffuse infiltration of the myocardium by lymphocytes with little alteration of the muscle cells.

JOHNSON.

Wakim, K. G., Gersten, J. W., Herrick, J. F., Elkins, E. C., and Krusen, F. H.: The Effects of Diathermy on the Flow of Blood in the Extremities. *Arch. Phys. Med.* 29:583 (Sept.), 1948.

The authors studied the effect of diathermy on the rate of peripheral circulation in a series of dogs and in a group of human subjects. Blood flow was determined in dogs by the use of a bubble flowmeter and in man, by the venous occlusion plethysmographic method.

The results indicated that diathermy produces a substantial increase in local circulation, particularly when applied directly to the extremity under study.

ABRAMSON.

Ziegler, R. F.: The Cardiac Mechanism During Anesthesia and Operation in Patients With Congenital Heart Disease and Cyanosis. *Bull. Johns Hopkins Hosp.* 83:237 (Sept.), 1948.

The purpose of this study is to determine the mechanism, significance, and management of cardiac arrhythmias occurring during anesthesia and operation in children with congenital heart disease and cyanosis and to determine the preterminal cardiac mechanism in the children who die during this period. Patients selected for the study included 175 consecutive children with congenital heart disease and cyanosis submitted to the Blalock-Taussig operation for the correction of the abnormal circulatory dynamics of pulmonic stenosis with an intracardiac right-to-left shunt. Similar electrocardiographic records were made in a control group which included fifteen patients in whom a patent ductus arteriosus was ligated; three patients in whom coarctation of the aorta was corrected surgically; and two patients who underwent resection of the pericardium for constrictive pericarditis.

The general incidence of the disturbances of the cardiac mechanism during anesthesia and operation in this series of children with congenital heart disease and cyanosis was approximately the same as the incidence in the noncyanotic group, where cyclopropane was the chief anesthetic agent. The author confirms the statement that the anesthetic agent is of greater importance than the type of operative procedure in the production of cardiac irregularities.

Arrhythmias of some sort occurred in approximately 80 per cent of the entire group of patients. Sinus tachycardia was found to occur during all stages of operation and could be attributed in many instances to the effect of atropine given either as routine preoperative medication or during the course of anesthesia and operation. Sinus bradycardia was most frequently observed under circumstances apparently favoring vagal stimulation, as evidenced by the fact that it was abolished in most cases by the administration of atropine. Ectopic arrhythmias occurred in more than one-half of the children. In forty-six (52.3 per cent), the disturbance reverted spontaneously to normal sinus rhythm; in nineteen (21.6 per cent), reversion was accomplished with atropine; in eight (9.1 per cent), the disturbance was unaffected by atropine; and in fifteen (17 per cent), the arrhythmia could not be classified. Nodal rhythm of various types occurred with nearly equal frequency during anesthesia and throughout all phases of operation and was not related to any specific operative procedure.

While direct vagal stimulation, as in mediastinal exploration and manipulation of the great vessels, may be responsible for the occurrence of such arrhythmias, they may also result from action of the anesthetic agent acting by way of the vagus nerves, as well as directly upon the myocardium and the specialized tissues of the heart. Morphine tended to exaggerate the arrhythmias, in part perhaps, by vagal stimulation, and atropine in the amounts usually given failed to protect the heart against irregularities produced by morphine. Morphine is claimed to have a protective effect against ectopic arrhythmias such as cyclopropane-epinephrine tachycardia.

Arrhythmias due to increased cardiac irritability, including premature systoles and paroxysmal tachycardia, occurred in a total of twenty-one patients (13.3 per cent).

Another type of disturbance of the cardiac mechanism, which can be detected only by electrocardiography, is the group of abnormalities of the form of the ventricular deflections.

In the terminal group were included seven children who died during anesthesia or operation, two children who experienced several episodes of cardiac asystole on the operating table and who died within twenty-four hours of cerebral thrombosis probably occurring during asystole, and one additional child whose operation was postponed after he had survived what was thought to be a series of preterminal arrhythmias during anesthesia. The terminal cardiac mechanism in each of the seven cases was cardiac asystole. Ventricular fibrillation occurred only once and in this case only after a prolonged period of asystole.

In every case except one, sinus tachycardia with a rate of 150 to 200 per minute preceded the onset of any other abnormality of the cardiac mechanism. Of much greater significance was marked bradycardia, either sinus or A-V nodal, which occurred in every case prior to terminal asystole. It seems evident that bradycardia, either sinus or nodal, with a rate of less than 50 per minute and with failure to respond to the administration of atropine, constitutes a specific warning of impending terminal asystole.

The author suggests that anoxemia is a factor of considerable importance. In support of this concept is the low average arterial oxygen saturation in the terminal group and the occurrence of other electrocardiographic abnormalities known to depend upon myocardial anoxia, as in coronary insufficiency with or without myocardial infarction.

During anesthesia and operation, stagnant anoxia, which may result from a failing circulation and which may, in turn, further depress the heart and circulation, should be benefitted by the action of cardiac stimulants such as epinephrine and digitalis. Should the heart dilate and stop, intracardiac injection of epinephrine has been one of the most widely recommended procedures. The danger of precipitating fatal ventricular fibrillation, especially during cyclopropane anesthesia, has been emphasized. Electrocardiographic evidence of this cardiac mechanism as a cause of death has been lacking in most human subjects and in this present study ventricular fibrillation never occurred even after the administration of large amounts of epinephrine. Greater value may be expected from the administration of a longer acting specific cardiac stimulant, such as digitalis, or by supplying the heart with essential materials for energy production, such as available oxygen, respiratory enzymes, electrolytes, etc., at the same time that the circulation is maintained by manual massage or the rhythmical stimulation of an artificial pacemaker.

The three children in whom the most marked changes in QRS occurred all had more complicated malformations than a simple tetralogy of Fallot; all three had severe congestive heart failure following the systemic-pulmonary anastomosis; and two died in less than one year after operation, the third surviving perhaps only because of ligation of her artificial ductus.

BELLET.

Cahill, G. F.: Pheochromocytomas. J. A. M. A. 138:180 (Sept. 18), 1948.

The author reviews his diagnostic and therapeutic experience with pheochromocytomas, presenting four of his cases in detail; he also discusses the observations of other investigators. He points out that although pheochromocytomas occur chiefly in the adrenal, they may also occur in pheochrome tissue in other parts of the body. Such extra-adrenal tumors occur intra-abdominally, for the most part, but instances of three such tumors located intrathoracically and one located intracranially have been reported. Although pheochromocytomas are seen particularly

in adults, with some predilection for females, a number have occurred in children. In nine per cent of cases in one series the tumors were considered to be malignant; in 9.7 per cent they were bilateral.

For diagnosis, the author places great faith in the benzodioxan test. This drug, 2-(1-piperidylmethyl)-1, 4-benzodioxan, is an epinephrine antagonist and when injected intravenously in the recommended dosage in cases of hypertension resulting from a pheochromocytoma, brings about a prompt and marked fall in the systolic and diastolic pressures with return to the prior pressure levels after fifteen minutes. No pressure changes occur with benzodioxan in hypertension of other types. The delineation of an adrenal pheochromocytoma radiographically with the aid of perirenal air insufflation for contrast and the x-ray demonstration of a tumor on urographic study are valuable diagnostic aids.

Surgical removal of the tumor is the only applicable therapeutic measure. Handling of the tumor before all its vessels have been ligated is dangerous because of the excessive quantities of epinephrine which may be expressed into the circulation. The intravenous use of epinephrine is of value when the drop in the blood pressure immediately following removal of a secreting tumor is of alarming magnitude, and adrenal cortical hormone may be needed if acute adrenocortical insufficiency results postoperatively. A rapid elevation of the systolic blood pressure to near its preoperative level within ten minutes after removal of a pheochromocytoma is an indication that a second functioning tumor is present.

HANNO.

Mendlowitz, M.: The Effect of Anemia and Polycythemia on Digital Intravascular Blood Viscosity. J. Clin. Investigation 27:565 (Sept.), 1948.

The author studied four patients with polycythemia and two with marked anemia. Digital blood flow, vascular resistance, and blood pressure were determined with the object of measuring blood viscosity.

Anemia tended to decrease, while polycythemia tended to increase blood viscosity. At the extremes observed, the viscosity was 80 per cent of normal at a hematocrit of 17 and 169 per cent of normal at a hematocrit level of 73.

WAIFE.

Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: The Effects of the Cardiac Glycosides Upon the Dynamics of the Circulation in Congestive Heart Failure. J. Clin. Investigation 27:588 (Sept.), 1948.

The newer techniques in cardiac physiology were used in a study of thirteen patients with varying degrees of heart disease in an attempt to determine the effects of the intracardiac injection of ouabain on the circulation. After venous catheterization ouabain was injected through the catheter over a period of one to two minutes in doses of 0.25 to 0.95 milligram.

In nine patients with clinical congestive failure, with low cardiac output, and an elevated right heart pressure the femoral arterial systolic pressure rose within a few minutes after ouabain injection, as did the mean and pulse pressures. Right ventricular and pulmonary arterial pressures were also increased. This group showed an increase in cardiac output. Peripheral venous pressure had not decreased at the time of the first increase in cardiac output in four of seven subjects so studied. In the other three patients circulatory pressure change had taken place before there was a drop in venous pressure.

In one to two hours variable pressure findings were noted which may be explained by alterations in blood volume or peripheral resistance. In three patients the cardiac output was unchanged or fell after ouabain. Two of these were not in clinical heart failure.

These authors conclude that ouabain acts directly on the failing heart by increasing its stroke volume; this action usually precedes cardiac slowing or any decrease in peripheral venous or right ventricular filling pressure.

WAIFE.

Book Reviews

THE CHEST AND THE HEART. By J. Arthur Myers, M.D., and C. H. McKinley, Ph.D. Springfield, Ill., 1948, Charles C Thomas, Publisher, 2 volumes, 1846 pages, with figures and tables. Price \$25.50.

Although the title of this two-volume work, "The Chest and the Heart," would lead one to believe that one volume is devoted to diseases of the lungs and the other volume to diseases of the heart, such is not the case. Volume I deals with disease of the chest in 1,021 pages. In Volume II, 308 pages are devoted to nonpulmonary tuberculosis and only 329 pages to the heart. It is, therefore, no wonder that the material presented on diseases of the heart is sketchy and incomplete. No attempt has been made to follow the generally accepted diagnostic scheme of the American Heart Association; actually each chapter, usually by a different author, follows its own pattern. We have, then, in effect, a series of short individual monographs rather than an integrated presentation of diseases of the heart. In spite of the restrictions in space, some of the authors of individual sections have done a remarkably good job. The roentgenology of the heart is ably presented by Ungerliedner and Gubner. Photographs of models of the heart assist greatly in explaining the many excellent roentgenograms which illustrate the chapter. Chapters on the physiology of the heart by Visscher, on our present knowledge and research on arterial hypertension by Page, on coronary artery sclerosis by Barnes, and on the physiological aspects of the electrocardiogram by Ashman are among the highlights in the book.

There is no section on clinical electrocardiography. The subject of cardiac arrhythmias is poorly presented, the electrocardiograms are not clear, and the frequent use of poorly chosen case reports makes this section rather hard to read.

The treatment of heart failure rightly emphasizes the importance of rest and the necessity for digitalis. However, the author of this section does not appear to be familiar with the literature on cardiac glycosides, because he speaks of digitoxin, Digoxin, and lanatoside C together, as though they were indicated in the same situations. He seems unaware of the extremely long latent period of digitoxin, because he advocates this drug intravenously (p. 1750) along with the other glycosides for the treatment of acute left ventricular failure. Nowhere are the differences in latent period or rate of dissipation of the individual glycosides discussed.

The author also does not seem to know that theophylline is combined with all mercurial diuretics now used because of its local tissue-protecting action. He says nothing of the anti-diuretic effect of morphine or Demerol. In discussing toxicity of mercurial diuretics, he omits the important point of possible idiosyncrasy to one of the mercurial diuretics, which, if not recognized, might lead to sudden death of the patient on the next injection.

Although the section on pulmonary surgery occupies twenty-five pages, cardiac surgery is dismissed quite casually in five pages.

It is evident that the editors of this book were primarily interested in diseases of the chest, and the section on the heart was added as an afterthought. This is indicated in their preface, where it is stated, "Originally this volume was intended to combine and bring to date two books published in 1927, namely, *The Normal Chest* and *Modern Aspects of the Diagnosis, Classification and Treatment of Tuberculosis*." Thus, we have an explanation of why tuberculosis of the genitourinary tract and even tuberculosis of the skin are forced into a book entitled "The Chest and the Heart." Since the heart is located in the chest, the editors were finally persuaded to in-

clude some discussion of the heart and grudgingly allowed less than one-fifth of the total space to the heart.

Since in the heart section there is much excellent material written by outstanding specialists in cardiology, it is hoped that a second edition will eliminate the sections on nonpulmonary tuberculosis from the second volume so that the entire second volume can be devoted to diseases of the heart. It is also hoped that the heart section will have its own editor (a cardiac specialist) who will be able to arrange the material so that there is included an adequate presentation of all phases of heart disease in an orderly and systematic manner. Some uniformity, then, will also apply as to bibliography. Now some sections, such as the section on arterial hypertension, are followed by an excellent, well-chosen set of references and others have no references at all.

ARTHUR C. DE GRAFF, M.D.

THE RENAL ORIGIN OF HYPERTENSION. By Harry Goldblatt, M.D. Springfield, Ill., 1948, Charles C Thomas, Publisher, 128 pages, 3 tables, and 38 figures. Price \$2.75.

The purpose of the American Lecture Series is to provide at moderate cost and in lasting, pleasing form authoritative dissertations on special topics. Dr. Goldblatt's book, *Experimental Renal Hypertension*, admirably fulfills the publisher's intention.

The work is shaped along the same line as the author's recent survey in *Physiological Reviews*. As such, it has the good and bad qualities of style favored by that journal. The good lies in a thoroughgoing exposition and integration of the author's work and of his conclusions as they now stand. The disadvantage is not at all serious for those who intend further study. It lies in a neglect of the fact that other workers, as is the author, are entitled to revise their views as new facts present themselves. Consequently, those who intend to devote to the field more than a deliberate study of this single volume will find themselves being more critical than a wider review would justify.

The style is clear, the illustrations pleasing, the clinical comments well restrained, and the whole is recommended to all who intend to read still a little further.

I. H. PAGE, M.D., AND A. C. CORCORAN, M.D.

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DR. H. M. MARVIN ELECTED PRESIDENT AT ANNUAL MEETING IN ATLANTIC CITY

Dr. H. M. Marvin, who has played a leading role in the affairs of the Association since its organization, was elected President for the 1949-1950 term at the Twenty-fifth Annual Meeting and Twenty-second Scientific Sessions held at the Haddon Hall, Atlantic City, the first week in June. Dr. Marvin, who is Associate Clinical Professor of Medicine at Yale University School of Medicine, succeeds Dr. Tinsley R. Harrison, of Dallas.

Chosen President-elect for the 1950-1951 term was Dr. Howard B. Sprague, of Boston, a former President of the New England Heart Association and member of the faculty of Harvard Medical School. Other officers elected are Dr. Edgar V. Allen, Rochester, Minn., Vice-president; Dr. John J. Sampson, San Francisco, Secretary (re-elected); and Grant Keehn, New York, Treasurer (re-elected).

At a meeting of the Board of Directors, A. W. Robertson, of Pittsburgh, was re-elected Chairman. Newly elected to the Board of Directors were: Arlie R. Barnes, M.D., Rochester, Minn.; Mrs. Douglas O. Burnham, Watertown, Conn.; George K. Fenn, M.D., Chicago, Ill.; Tinsley R. Harrison, M.D., Dallas, Texas; John C. Higgins, Vancouver, Wash.; T. Duckett Jones, M.D., New York, N. Y.; Louis N. Katz, M.D., Chicago, Ill.; Robert L. King, M.D., Seattle, Wash.; Rustin McIntosh, M.D., New York, N. Y.; Douglas B. Marshall, Houston, Texas; Frank L. Mechem, Seattle, Wash.; David D. Rutstein, M.D., Boston, Mass.; John J. Sampson, M.D., San Francisco, Calif.; Russell Stover, Kansas City, Mo.; C. J. Van Slyke, M.D., Washington, D. C.; Robert W. Wilkins, M.D., Boston, Mass.; Irving S. Wright, M.D., New York, N. Y.

The Annual Membership Meeting which named the officers of the Association (Board members are chosen by the Assembly) also elected the following to the Assembly, the over-all governing body which includes both lay and medical members:

Listed regionally:

New England

O. Kelley Anderson, Boston, Mass.
Julian Anthony, Boston, Mass.
Laurence D. Chapin, M.D., Springfield, Mass.
Paul K. French, M.D., Burlington, Vt.
John H. Frye, Jr., Portland, Maine
Marshall N. Fulton, M.D., Providence, R. I.
Vlado A. Getting, M.D., Boston, Mass.
John H. Miller, M.D., Laconia, N. H.
Henry Utter, M.D., Providence, R. I.

East

James N. Brittain, Philadelphia, Pa.
Irvin M. Cook, Baltimore, Md.
Albert D. Kaiser, M.D., Rochester, N. Y.
Charles A. Poindexter, M.D., New York, N. Y.

South

Harold Green, M.D., Winston-Salem, N. C.
Arthur Grollman, M.D., Dallas, Texas
Edgar Hull, M.D., New Orleans, La.
Douglas Marshall, Houston, Texas
George R. Meneely, M.D., Nashville, Tenn.
John F. Phillips, Albany, Ga.
William C. Stewart, M.D., Charleston, W. Va.
C. J. Van Slyke, M.D., Washington, D. C.
Wallace M. Yater, M.D., Washington, D. C.

Great Lakes

Claude E. Beck, M.D., Cleveland, Ohio
Alva Bradley, Cleveland, Ohio
John F. Briggs, M.D., Minneapolis, Minn.
S. J. Collins, Youngstown, Ohio

Kurt Stubenvoll, Eau Claire, Wis.
 Stanley Dorst, M.D., Cincinnati, Ohio
 A. Carlton Ernstene, M.D., Cleveland, Ohio
 Herman C. Krannert, Indianapolis, Ind.
 Sidney Strauss, M.D., Chicago, Ill.
 Charles E. Wilson, Detroit, Mich.

Midwestern and Mountain

Clarence Beck, Emporia, Kan.
 John Lucien Calene, M.D., Aberdeen, S. D.
 Hans H. Hecht, M.D., Salt Lake City, Utah
 Palmer Hoyt, Denver, Colo.
 Fred G. Jenkins, Kansas City, Mo.
 Robert N. Larimer, M.D., Sioux City, Iowa

Frederick W. Niehaus, M.D., Omaha, Neb.
 Russell Stover, Kansas City, Mo.

West

John Martin Askey, M.D., Los Angeles, Calif.
 Philip Bailey, Seattle, Wash.
 Max Hemingway, M.D., Bend, Ore.
 S. P. Lucia, M.D., San Francisco, Calif.
 Robert C. Manchester, M.D., Seattle, Wash.
 E. B. McNaughton, Portland, Ore.
 Donald S. Munroe, M.D., Vancouver, B. C.
 S. M. Poindexter, M.D., Boise, Idaho
 John W. Scott, M.D., Edmonton, Alberta
 Donal R. Sparkman, M.D., Seattle, Wash.

GOLD AWARDS GIVEN AT ANNUAL DINNER

The Atlantic City sessions included Annual Meetings of the Scientific Council and of its Section on the Circulation, as well as of the American Council on Rheumatic Fever. Preceding these was a two-day organization meeting of the Staff Conference of Heart Associations, a newly formed group comprising the professional staff workers in the affiliates of the American Heart Association.

Two Scientific Sessions, followed by three panel discussions, were held at which nineteen papers were presented and a number of others were read by title only. Dr. George E. Burch, New Orleans, was Chairman of the panel discussion on Management of Congestive Failure and Importance of Low Sodium Diet. A second panel on Congenital Heart Disease was presided over by Dr. Alfred Blalock, Baltimore. Dr. Edgar V. Allen, Rochester, Minn., was Chairman of the panel on Anticoagulant Therapy.

The newly created Gold Award, symbolized by a certificate and a gold medallion in the form of the Association's symbol, was presented at the Annual Dinner to nine major contributors to the success of the 1949 National Campaign.

Harold E. Stassen, President of the University of Pennsylvania and National Campaign Chairman in 1949, was the first recipient of the Gold Award, presented to him by Dr. Marvin, the incoming President. Mr. Stassen in turn presented Gold Awards to William E. Cotter, Executive Vice-chairman of the February campaign; Mark Woods, Chairman of the Public Relations Committee; Sylvester L. Weaver, Jr., Chairman of the Radio and Television Committee, and Raoul E. Desvernine, Chairman of the Men's Committee. Recipients of the Gold Award in absentia were Miss Irene Dunne, Women's Committee Chairman; Maurice J. Tobin, Secretary of Labor, Chairman of the Labor Committee; Juan T. Trippe, Chairman of the Corporations Committee, and Ralph Edwards, of the "Truth or Consequences" radio program.

Representative Walter H. Judd, Member of Congress from Minnesota and also a physician, addressed the Annual Dinner on "Trends in International Affairs." Mr. Stassen gave an interim report on the 1949 National Campaign and announced that \$2,850,000 had been raised at the time of the Annual Meeting, with additional increments expected.

The Staff Conference of Heart Associations was addressed at its organizational meeting by Professor Ira V. Hiscock, Chairman of the Department of Public Health, Yale University School of Medicine, and by Dr. Alan Gregg, Director for the Medical Sciences, Rockefeller Foundation.

AMERICAN LEGION AID CITED AT MEETING OF AMERICAN COUNCIL ON RHEUMATIC FEVER

The generous action of the American Legion and the American Legion Auxiliary in lending valuable assistance to the Association at a critical time was high-lighted at the annual meeting of the American Council on Rheumatic Fever. In a résumé of the Council's activities since January 1, 1948, special attention was given to the American Legion Fund of \$50,000, contributed jointly by the Legion and Auxiliary at a time in 1946 when the grant served as a catalyzing agent to stimulate broadening of the Association program.

It was reported that the fund was fully expended or allocated as of February 28, 1949. One-half of the fund (\$25,000) was utilized in two three-year fellowships granted to Dr. Joseph E. Warren, of the House of the Good Samaritan, Boston, and Dr. Samuel T. Schlamovitz, New York University College of Medicine, for research in rheumatic fever. Dr. Warren has subsequently been awarded a research fellowship by the Association for continuation of his studies. Reports by both American Legion fellows were presented at the Atlantic City meeting.

The remainder of the Legion Fund was expended for staff assistance, permitting continuity of operation of the Council during a difficult period of reorganization of the American Heart Association.

BOARD APPROVES \$6,000,000 GOAL FOR 1950; HAWAII HEART ASSOCIATION ADMITTED TO AHA

The Executive Committee of the Board of Directors at its April meeting approved a proposed budget for 1950 which included plans for a 1950 fund-raising campaign with a goal of \$6,000,000.

The Board voted to amend the Association's certificate of incorporation to permit activity in "other related fields of medicine and research or through other health organizations." The permissible number of Directors was also raised to 100, with by-law change to set the actual number at sixty instead of forty as at present.

The President was authorized to appoint a committee to study the possibilities of effecting a merger with the Society for the Study of Arteriosclerosis as a Section of the Scientific Council of the American Heart Association.

The Association's farthest-away affiliate was admitted to the AHA family with the Board's approval of the application of the Hawaii Heart Association.

COURSE IN ELECTROCARDIOGRAPHY

The annual intensive two-week course in electrocardiography for *graduate physicians* will be given at Michael Reese Hospital in Chicago, under the personal direction of Dr. Louis N. Katz, Director of Cardiovascular Research, from August 15 to August 27, 1949, inclusive. Group and individual instruction will be given, and the course is open to beginning and advanced students in electrocardiography. The course will meet daily from 8:00 A.M. to 5:00 P.M. Tuition fee is \$150.00.

Further information and a copy of the lecture schedule may be obtained on application to Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, Twenty-ninth Street and Ellis Avenue, Chicago 16, Illinois.

American Heart Journal

VOL. 38

AUGUST, 1949

No. 2

Original Communications

ON CERTAIN ASPECTS OF THE NATURE AND TREATMENT OF OLIGEMIC SHOCK*

IRVINE H. PAGE, M.D.

CLEVELAND, OHIO

GEORGE BROWN was the friend of us all. It is proper that as we grow older in the science of medicine we should constantly freshen the remembrance of those who preceded us in the making of that science. George Brown was one to be remembered. Were he here he would cast a wry smile at my floundering in an already confused field. But it was just such things he liked to do.

So with another wry smile, let us consider some limited aspects of shock, with some simplifying, and, I hope, clarifying dogmatism, as I think Brown himself would have enjoyed doing.

Over the past nine years, I have followed the literature on shock and I have read a majority of the older papers. I have come away with three definite impressions: (1) The search for the initiating mechanism of oligemic shock is probably ended after many false starts. (2) Until recently, the field has been lacking in painstaking work verifying or rejecting many brilliant suggestions concerned with the mechanism of shock. (3) Most investigators have concentrated on the role of one organ or system, to the implied exclusion of others.

The nervous system, the adrenal glands, the heart, the liver: all have had their day, to be supplanted after a barely decent interval by another organ or system. But on one fact all investigators are agreed: shock represents all-embracing dissolution. Therefore, its over-all effects can probably best be measured by a quotient representing cardiac output and oxygen consumption as a measure of effective blood flow. Gesell,¹ it seems to me, has most nearly approached this concept within his "nutrient flow." He assumes that in shock, transport of nutrient material and carrying away of waste are interfered with,

From the Research Division of the Cleveland Clinic Foundation.

*The George Brown Memorial Lecture. Read at the Twenty-first Annual Scientific Meeting of The American Heart Association, Chicago, Ill., June 18-19, 1948.

either by dilution of the blood or by reduction of flow. Since the effective blood flow is seriously reduced for prolonged periods of time, it is not surprising that widespread damage occurs. Whether the lack of one specific element, such as oxygen, is chiefly at fault, or whether many substances are involved, is not known. For reasons such as these, it is probably unwise to continue the exclusive use of the terms anoxia or hypoxia to explain the cause of the tissue changes. Whatever the mechanism, widespread tissue ischemia of sufficient persistence results in shock. I must add one other impression from the literature: Carl Wiggers in his several reviews beginning in 1903 has maintained, perhaps as much as anyone, that judicial balance representative of the best in the trained scientific mind.

Let me illustrate from one of our patients how our own interest in these problems was aroused. This example also shows that blood pressure may be excessively low, but so long as no tissue ischemia occurs, shock does not appear.² This unfortunate patient had taken 15 Gm. of arsenic trioxide with suicidal intent. Three hours later his arterial pressure was 65/35, and twelve hours later, 45/0, and his pulse was 98 beats per minute. Curiously, while he was on the stretcher his mind was relatively clear despite the low pressure; and, importantly, his skin was warm and well perfused. Measurement showed that cardiac output had doubled while the calculated peripheral resistance remained very low. Thus, he overcame the handicap of low arterial pressure by increasing the volume output of the heart and decreasing peripheral resistance, and so avoided ischemia of the tissues and shock. Within twenty-four hours, his blood pressure had returned to normal.

It is instructive to examine the results of basal blood flow measurements in tissues, in relationship to blood pressure. Gesell gives a good example from studies in the submaxillary gland (Fig. 1).

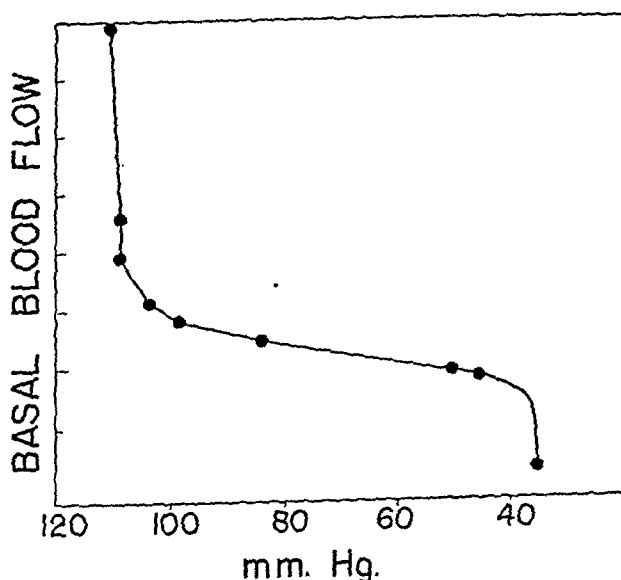


Fig. 1.—Relationship of basal blood flow to arterial pressure in the submaxillary gland. The marked fall in blood flow early and late is especially to be noted. (From Gesell, A.: *Am. J. Physiol.* 47:438, 1918-1919.)

As the first 10 to 20 mm. fall in blood pressure takes place, a profound reduction of organ blood flow occurs, at least in such nonessential organs as the submaxillary glands. The curve of fall then remains almost level during the next fall of 50 mm. and again falls off sharply at 40 mm. mean pressure. Perhaps the most dangerous of these periods is the first, because blood pressure appears to be "well maintained," yet tissue perfusion has fallen off sharply. All observers recognize the danger of arterial pressures below 50 mm. Hg and will attempt their elevation, but not so with the lesser degrees of hypotension. This relationship of blood pressure and blood flow has been formalized in the highly significant work of Norman Freeman, which will be discussed later.

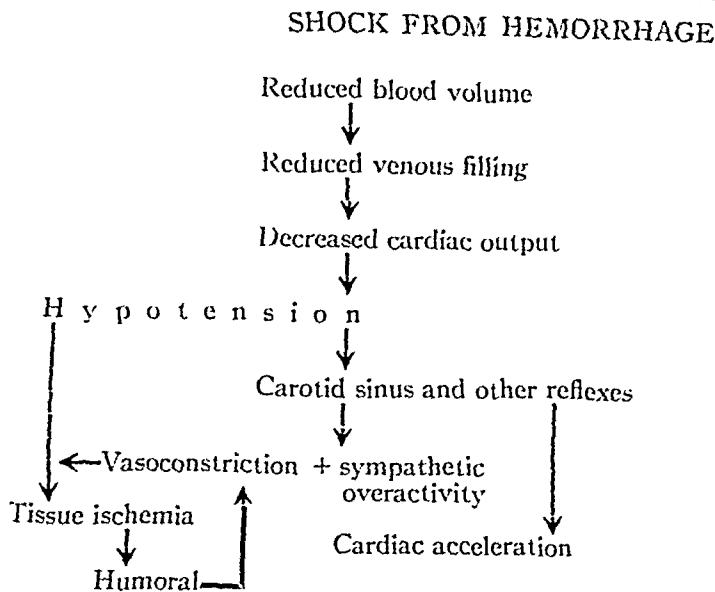
It has taken possibly thirty years to recognize fully the importance of oligemia as a cause of shock. As with so many important discoveries, many investigators have contributed, and years have been required for final acceptance of their findings. Clinicians probably realized its importance first, but did nothing about it except attempt to measure it by the uncertain hemoglobin or hematocrit methods. Henderson, Robertson, and Bock⁵³ and Keith⁵⁴ were the first to measure the decrease by dye dilution methods. Subsequently much critical work has been performed. Of especial importance have been Blacklock's⁵ and Phemister's⁴ demonstrations that loss of plasma at the site of injury often is sufficient to cause shock. Most investigators would now agree that this is not the only factor in the production of shock, but is certainly of prime importance. During World War II, Gregersen⁵ and Gibson⁶ did much to add more accurate quantitative data to this aspect of the problem. Another vital demonstration was that in shock cardiac output is low. It is difficult to ascertain precisely when this concept originated. Certainly, many had believed it for some time. By 1923, Cannon could say in his monumental book on shock, "This theory starts with the now well-known fact that the low blood pressure in shock is due to the small amount of blood pumped out by the heart." Since that time, many investigators have confirmed this finding in animals. Cournand, Richards, and their associates⁷ extended the observation to man by use of the modern cardiac catheterization technique.

These observations, along with low blood pressure, give the picture of the state of affairs early in shock. The oligemia may be given primacy; the rest follows. (Table I.) Then begins the period of generalized dissolution in which so many chemical reaction paths are disturbed as to leave the investigator both baffled and frustrated. One must have sympathy for the biochemists catapulted into the problem of shock during the war lest they fail in their patriotic duty. This, it seems to me, is richly reflected in the admirable review of Wilhelmi,⁸ yet sympathy fails to yield a satisfying degree of clarity. Changes there are, and many of great magnitude, but they are everywhere. To separate the important from the unimportant seems beyond contemporary understanding, at least any that I have encountered.

Clearly the pleasures of fresh adventure have been enjoyed but little in the past years. While much knowledge has been refined, the concentrate, I fear, has lost some of its original essence. We are likely, as it were, to mistake one solar system for the galaxy.

The more important practical clinical aspects of oligemic shock will not be touched on, since it is the part of wisdom to leave these to those with large battle experience, such as McMichael⁹ and Sharpey-Schafer¹⁰ in England, and Henry Beecher in this country.

TABLE I. KNOWN MECHANISMS IN OLIGEMIC SHOCK



I shall now touch on several problems that have been of especial interest to us. The first of these is concerned with the producing of experimental oligemic shock with some degree of reproducibility. Next, the occurrence of vasoconstriction, and some of the mechanisms by which it may be produced, will be considered. There follows a brief discussion of investigations into some factors influencing survival after experimental shock, such as blocking the autonomic ganglia and changing the reactivity of the blood vessels to stimuli. Finally, treatment of late shock by intra-arterial blood transfusion is described. With this outline in mind, perhaps some slim thread of continuity will be discerned.

PRODUCTION OF EXPERIMENTAL OLIGEMIC SHOCK

I shall touch on this problem only briefly. Glasser and I¹¹ have studied the problem for the past three years, attempting to find a "standard" method. The best we have been able to do is to define the limitations of present methods. We employed a modification of that of Wiggers and Werle,¹² in which blood is removed until the pressure is brought to 50 mm. Hg and kept there for ninety minutes. It is then lowered to 30 and held there for forty-five minutes. The blood was taken into a reservoir arranged so that the pressure within it could be kept constant. The reservoir was suspended on springs, and a writing lever attached to record the filling weight on a kymograph (Fig. 2). It was connected to a femoral artery and the connection kept open so blood could flow in or out as the arterial pressure was greater or less than that in the reservoir.

At the end of the 135-minute period of hypotension, following the method employed for the same purpose by Kohlstaedt and Page,¹³ blood was transfused intra-arterially until the pressure reached the control level. We found, just as they had, that only about one-half to two-thirds of the blood was necessary to restore the pressure to control levels.

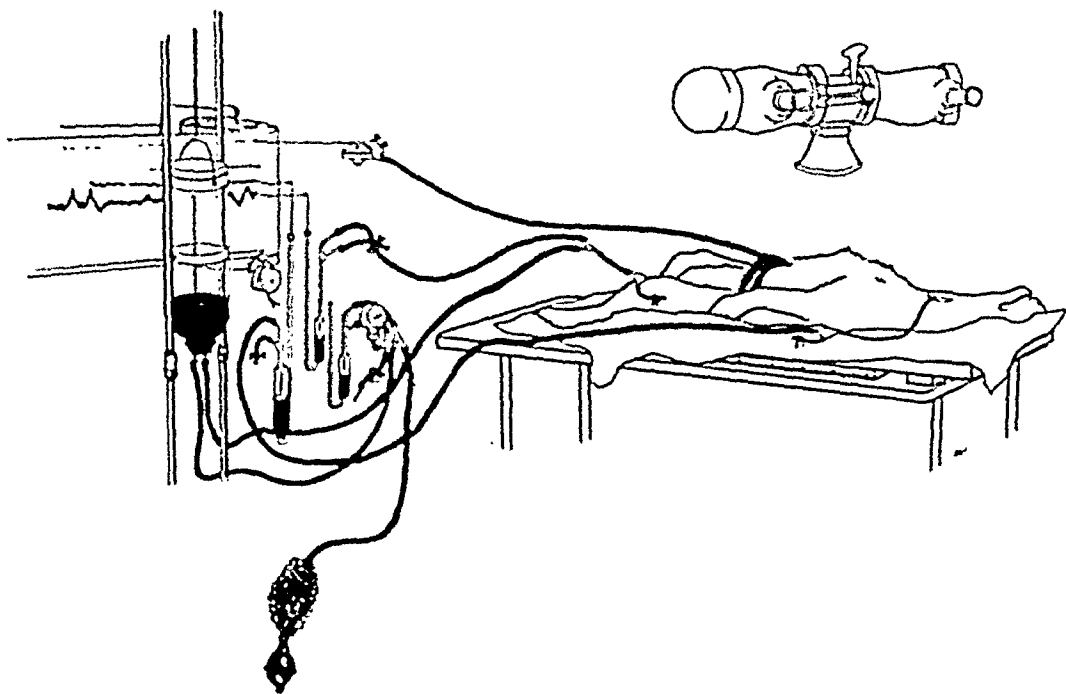


Fig. 2.—Apparatus for bleeding and arterial transfusion. The pressure reservoir is suspended on springs and its movements recorded on the kymograph by an ink-writing pen. Arterial and venous pressures and respiration are recorded.

It soon became apparent that there were wide limits within which the animals died or survived. By survival is meant unlimited survival, not survival for merely twelve or twenty-four hours. The variability was so great that we found it necessary to seek for objective criteria which would give us some clue as to whether the animals would survive or not.

Page and Kohlstaedt^{13,14} had employed two such criteria: (1) the return of the pressor response to angiotonin or adrenalin to its control level after retransfusion, and (2) the degree of cardiac dilatation that had occurred. We were able to confirm both, but the amount of equipment necessary for accurate measurement of cardiac size militated against its general usefulness.

The curves traced by the record of the inflow and outflow of blood from the pressure reservoir gave us a criterion of great usefulness. If during the hypotensive periods, the arterial pressure tended to fall off and blood to flow back into the animal (Figs. 3 and 4), it could be shown that prognosis was poor. Further, if all the blood removed was required to restore the level of arterial pressure to its control level, prognosis was also poor. Thus, the re-

sponse to adrenalin, the continued uptake of blood by the animal, especially during the drastic hypotensive period, and the amount of blood required by arterial transfusion to restore the control pressure, when considered together, provided criteria of significant accuracy.

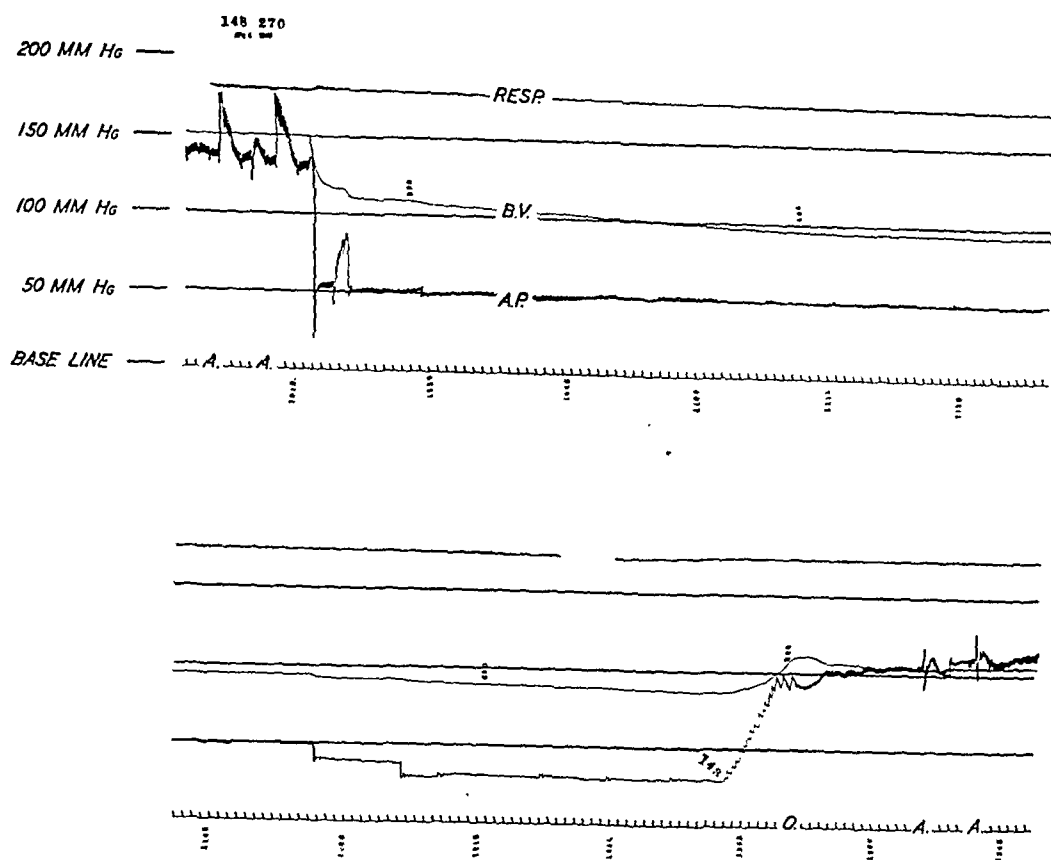


Fig. 3.—Record of dog with good prognosis after hemorrhage. Reading from above down (1) respiration, (2) weight of blood in reservoir, (3) arterial pressure, (4) time in minutes. A signifies adrenalin injection; O signifies ouabain injection. Note the lack of intake of blood during hypotensive period of 143 minutes, the small uptake to restore arterial pressure to control levels, and the return of adrenalin responsiveness.

During the first year of the work, survival among the dogs with poor prognosis was only 7 per cent, and among those with good prognosis, 35 per cent. This was well after the time that simple technical inadequacies had made themselves felt. Everyone recognizes that after the first dozen or so experiments technique has usually improved sufficiently to increase the percentage of survival, but the circumstances were different in our experiments. For no apparent reason, sometime early in the second year of experimentation a great many more animals fell into the group with good rather than poor prognosis. At that time 84 per cent of the animals had a good prognosis and correspondingly fewer had a poor one. This ratio was maintained to the end of the experiments, with, however, several weeks, and often months, of notable exceptions. During these periods, without warning a large percentage of the control dogs failed to survive and the percentage of survival returned to that of the first year (Fig. 5). We have investigated a variety of possible causative

factors in the hope that some clue to this most remarkable behavior might be found. But we have failed to find one. The importance of the phenomenon lies in the fact that survival can be so profoundly influenced by factors entirely outside our control. When the number of animals with good prognosis

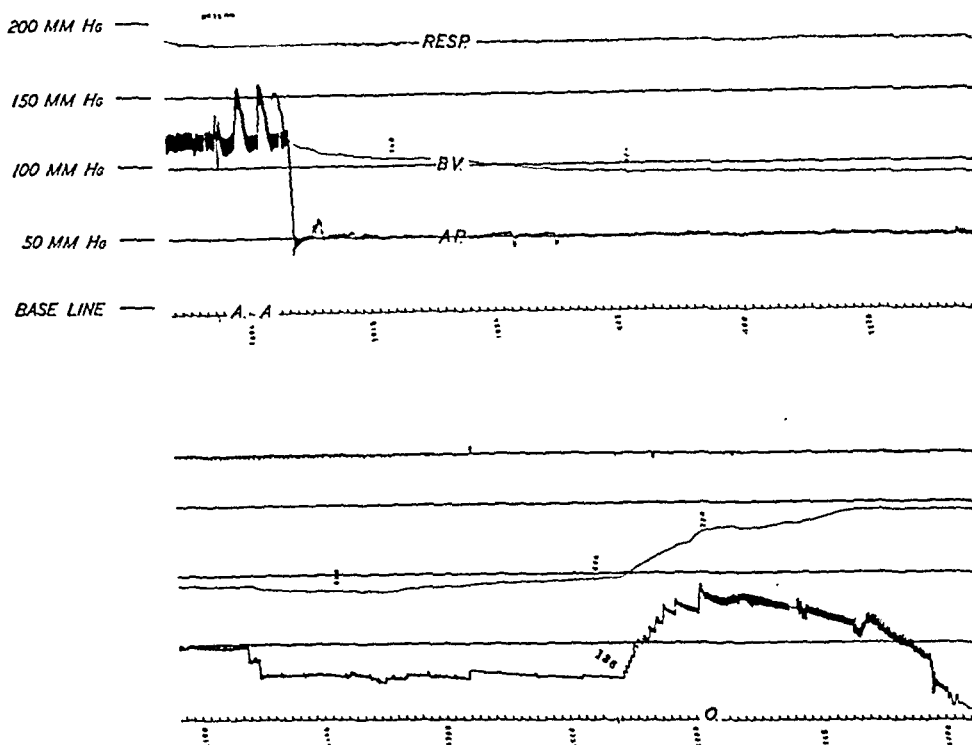


Fig. 4.—Record of dog with poor prognosis after hemorrhage. Symbols as in Fig. 3. Note the intake of blood during the latter part of the hypotensive period, large intake to restore blood pressure to control level, and poor return of response to adrenalin.

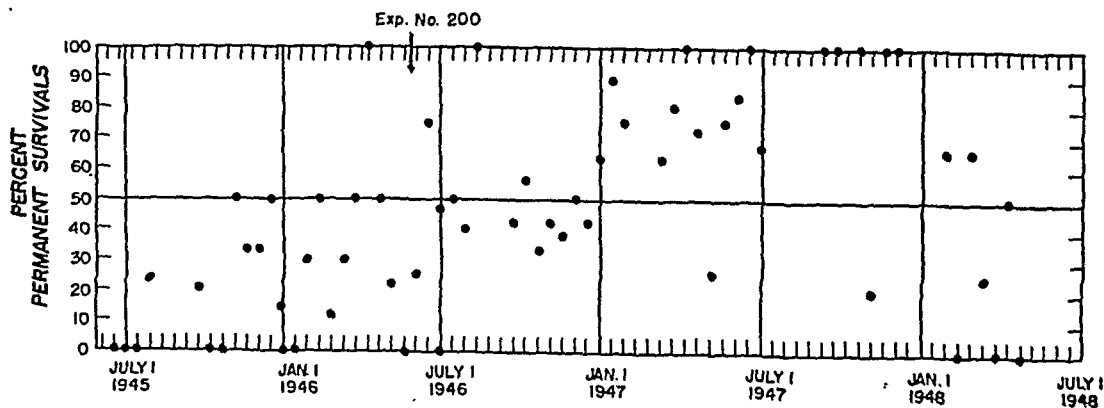


Fig. 5.—Percentages of permanent survival after shock procedure for two-week periods from July, 1945, to June, 1948. No division is made between those with good or poor prognosis. (From Glasser, O., and Page, I. H.: *Am. J. Physiol.* **154**:297, 1948.¹¹)

rises from 35 to 84, it is evident that something in the mechanism has eluded us and that this something is of the greatest importance. The second reason that the recognition of the phenomenon is important is that in serial experiments

where uniformity of behavior is expected, it may not occur. Animals with good prognosis cannot fairly be compared with those of poor prognosis. This distinction seems of real importance. Thus, the hope that there is such a thing as regularly reproducible "standardized" shock seems to be only statistically true, and then only when a sufficient number of experiments have been performed over a long enough period. We have studied the shock procedure in 482 dogs to obtain this information. This may seem a great many for such uninspired knowledge, yet it seems to me to pose one of the fundamental problems in the field of shock.

VASOCONSTRICTION IN SHOCK

The problem of vasoconstriction in shock, viewed superficially, seems relatively simple. But closer analysis reveals extraordinary complexity, and despite much good work, there is still no satisfying answer. I shall deliberately avoid the problem of the relationship of vasoconstriction to peripheral resistance, thereby freeing myself of a great and controversial burden. It is a problem that the masters of hemodynamics such as Wiggers, Visscher, and Hamilton refuse to answer categorically.

What, then, are the caliber changes in the small and smallest vessels in various parts of the vascular tree during the different stages of shock? Probably depending on the method of examination, the published results indicate vasodilatation in some investigations and vasoconstriction in others. Where tissues were manipulated and exposed, or the natural blood supply altered by transfusion, vasodilatation was usually observed. When these were avoided, vasoconstriction seemed to occur. I shall not trouble you with a recitation of the many important contributions to this problem, but rather take the speaker's prerogative of presenting the work in which he has participated.

Dr. Richard Abell and I¹⁵⁻¹⁷ employed the elegant method of Clark and Zintel, in which the exteriorized gut and its mesentery are placed in an observation chamber sewn into the belly wall. This allowed the tissues to be examined at any time with little disturbance to the animal. Cats, dogs, and rabbits were studied under pentobarbital anesthesia after tourniquet, burn, and hemorrhage.

The following course of events was observed (Fig. 6). Marked constriction of the arteries and arterioles occurred usually within an hour after, for example, incomplete occlusion of the limbs, lasted several hours, and finally gave way to relaxation an hour or more before death. The constriction was associated with reduced blood supply to the mesentery and intestine, and with reduced venous return from them. The veins of the mesentery also became constricted, but showed less tendency to dilate as death approached. The lymphatics were likewise narrowed. With severe hemorrhage, the same effects were observed, but the vasoconstriction occurred more promptly. The vasoconstriction after hot water burns also was very severe, and, as after the other shocking procedures, preceded by some time the fall in arterial pressure. The

closing of arteriovenous anastomoses further reduced the return of blood to the right heart but aided the capillary circulation.

There seems to be little disagreement that the vessels of the limbs are constricted. This is particularly striking in patients, and led Freeman to the correct clinical view that simple observation and palpation of the extremities is usually the most useful sign of shock. Recent work of Wiggers, Opdyke, and Johnson¹⁸ leaves little doubt that resistance to blood flow is increased in the liver, a highly important vascular bed, especially in the dog because of its somewhat unique valvular arrangement. The increase in resistance may well account for the intestinal bleeding so commonly seen in dogs after shock, but rare in human beings. The spleen is also the source of some increase in resistance. Mesenteric resistance also increases during hemorrhagic hypotension (Selkurt, Alexander, and Patterson¹⁹). The only important area so far studied in which resistance decreases rather than increases is the coronary circulation, according to Opdyke and Foreman.²⁰ During hemorrhagic hypotension, coronary flow decreased to 30 to 60 per cent of the control flow, and flow resistance was greatly decreased. Following reinfusion of all of the withdrawn blood, coronary flow increased 121 to 420 per cent of the control. Vasodilatation appeared to play a prominent part in the decrease in resistance.

Vasoconstriction in the kidneys is of very especial interest to Corcoran and myself and will therefore be reviewed in somewhat more detail than the other vascular beds. There is a very practical reason for doing this, as well. Treatment of shock has so much improved that a not inconsiderable number of patients are kept alive long enough to die of the renal effects of shock rather than of the shock itself. The work I shall now report is chiefly due to Corcoran; started in 1939, it was later carried on under contract with the Office of Scientific Research and Development.

SHOCK AND THE CRUSH SYNDROME

When one organ receives almost one-fourth of the total cardiac output, it is not difficult to understand why this interests greatly those concerned with the problem of shock. The kidneys receive just about this amount.

The renal blood flow decreases sharply after hemorrhage, with a disproportionate decrease in glomerular filtration in dogs (Corcoran and Page,²¹ Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke,²² Selkurt²³), and in human beings (Lauson, Bradley, and Cournand²⁴). Repeated prolonged hemorrhage decreases the ability of the kidneys to respond to transfusion by restoration of control blood flow and filtration rate (Fig. 7). The explanation of this vasoconstriction, so intense, early, and persistent, seems to be partly humoral and partly nervous. Which is the more important, we are at present unable to say. That the decrease in blood flow is not due to decrease in arterial pressure alone is shown by the observation²⁵ that reduction of blood flow during the onset of shock due to partially occluding tourniquets occurs well before pressure falls, as will be seen in Fig. 8.

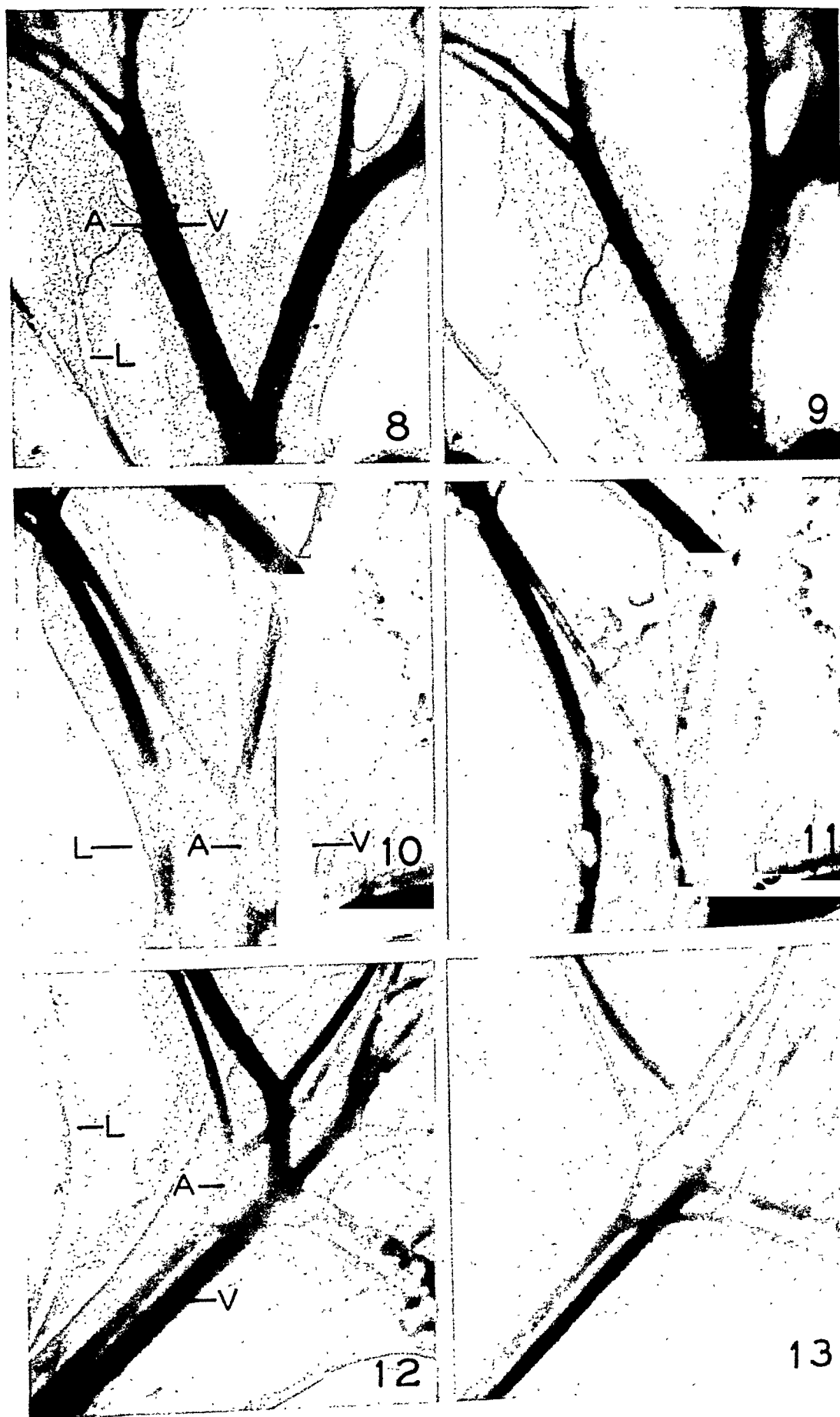


Fig. 6—See opposite page for legends.

You will all recall that the term crush syndrome became common during World War II. Actually, the crush syndrome had been seen and described during World War I. But Bywaters and Beall,²⁵ in 1941, were the first to investi-

EFFECT OF BLEEDING AND TRANSFUSION ON RENAL FUNCTION

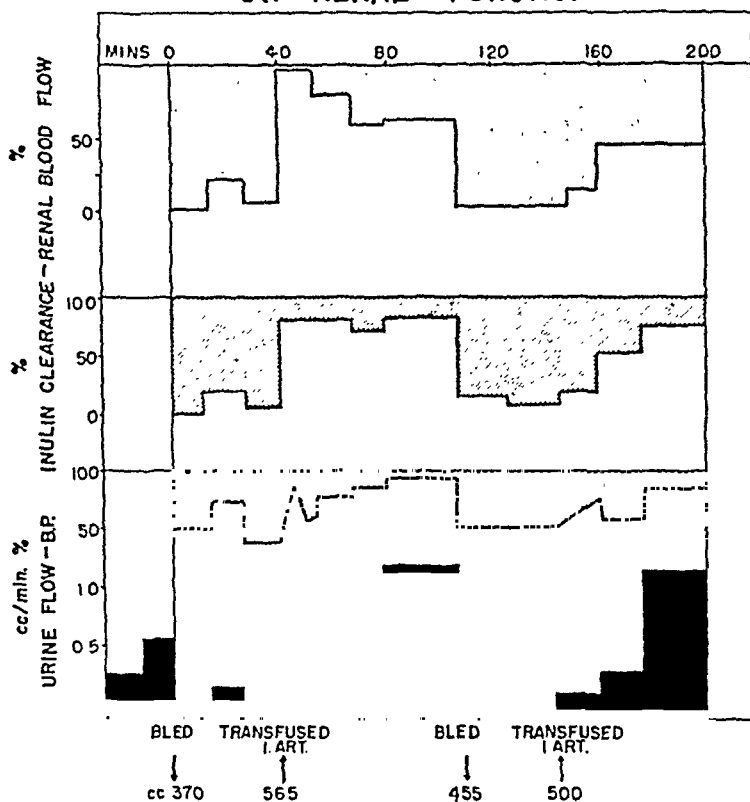


Fig. 7.—The effect of bleeding and arterial transfusion on renal blood flow, glomerular filtration, blood pressure, and urine flow. After the second bleeding, the persistent ischemia of the kidneys is evident.

Fig. 6.—Photographs of blood and lymphatic vessels in intestinal-mesentery chambers in anesthetized cats.

8, Control photograph of vessels in a portion of the mesentery of an adrenalectomized cat (Cat 11). Both adrenal glands had been removed three hours and twenty minutes before. This photograph was taken at 2:20 P.M. The pressure at this time was 136 mm. Hg ($\times 3.6$).

9, The same vessels shown in 8, at 3:37 P.M. Pressure 70 mm. of mercury. The cords were tied on the legs at 3:12 P.M. The arteries are constricted and the veins and lymphatics narrowed. The cat died in shock at 9:15 P.M. ($\times 3.6$).

10, Control photograph of vessels in a portion of the mesentery of a nephrectomized cat (Cat 9) taken at 11:29 A.M. Pressure 120 mm. of mercury. The kidneys were removed the day before this photograph was taken. A, artery; V, vein; L, lymphatic ($\times 6.3$).

11, The same vessels as shown in 10, at 3:37 P.M. Pressure 70 mm. of mercury. The cords were tied on the legs at 11:52 A.M. and were cut at 3:19 P.M. The arteries are constricted and the veins and lymphatics narrowed. The cat died in shock at 5:10 P.M. ($\times 6.3$).

12, Control photograph of blood vessels in a portion of the chamber. This photograph was taken at 1:07 P.M. Pressure 84. mm. Hg ($\times 6.3$).

13, The same vessels as in 12, after 32 c.c. of blood had been drawn from the femoral vein. This photograph was taken at 3:42 P.M., and the pressure at this time was 110 mm. of mercury. The blood was drawn as follows: 10 c.c. at 1:38 P.M.; 10 c.c. at 2:15 P.M.; 12 c.c. at 3:40 P.M. The arteries are constricted and the veins and lymphatics narrowed ($\times 6.3$).

(From Page, I. H., and Abell, R. G.: J. Exper. Med. 77:215, 1943.¹⁵)

gate seriously the nature of the problem. Their contributions were of major importance. As this matter became more important during the war, especially because of air raids, many others took up the investigation. I do not wish to divert your attention too long from our main thesis, the shock problem; nevertheless, it is worth viewing the renal problem of shock as an integral part of shock itself.

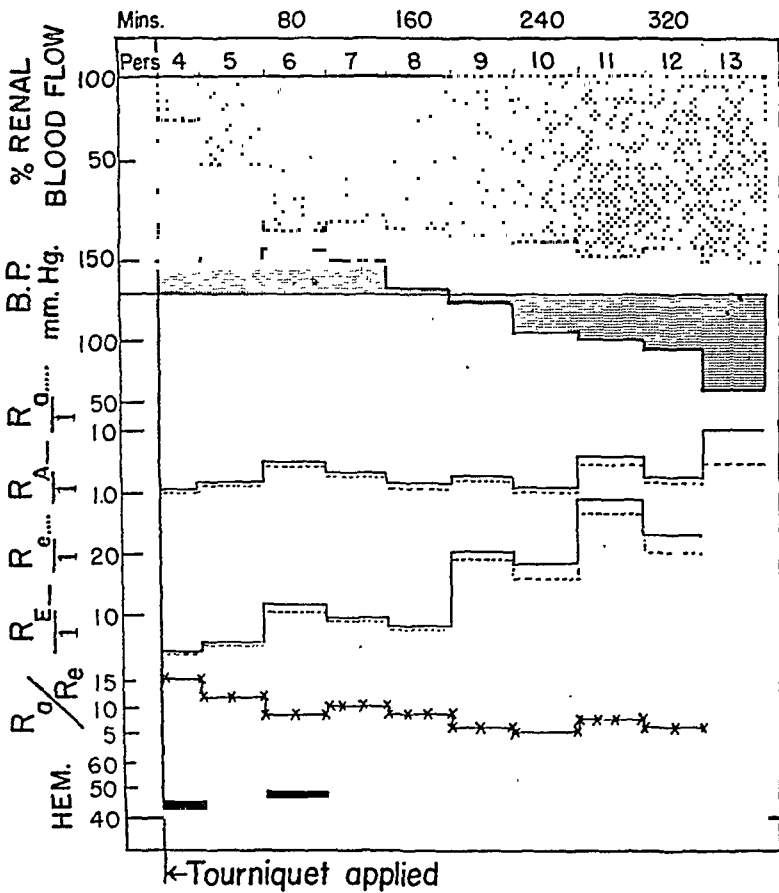


Fig. 8.—Effect of tourniquet application on total renal blood flow and blood pressure. Calculated renal resistance and hematocrit of resistance (R) are shown as ratios of the control level, which is taken as equal to 1; R_A , total afferent arteriolar resistance; R_a , the same corrected for changes of blood viscosity; R_E , total efferent arteriolar resistance; R_e , the same corrected for viscosity. The ratio R_a/R_e expresses the relative changes of arteriolar resistance proximal and distal to the glomeruli. Hem. = hematocrit index. (From Corcoran, A. C., Taylor, R. D., and Page, I. H.: Ann. Surg. 118:871 1943.²⁵)

Corcoran and I^{27,28} have reviewed the literature in some detail elsewhere, and I refer you also to some excellent review articles, covering special phases of the subject, by Macgrath,²⁹ Lucké,³⁰ Mallory,³¹ and Moon.⁵⁷ Regarding the experimental investigation, suffice it to say here that we have been able to produce renal lesions in rats which leave little to be desired as reproductions of the human syndrome. It was always necessary to produce shock in the rats before injecting a solution of myoglobin to produce the lesions. Experimental crush syndrome thus seems due to coexistence of severe renal ischemia, hypotension, and myoglobinuria. The conditions of pigmentary precipitation (aciduria, oliguria) are met, while the kidneys are further damaged because of

lack of blood flow. There are doubtless many other mechanisms leading to much the same result, but a recitation of these would lead us too far afield.

Treatment obviously consists first in remedying the shock, thus re-establishing some degree of urine flow. The lessening of toxic absorption from the area of injury and of loss of plasma into it by pressure bandages, and the establishment of a rapid rate of urinary flow by administration of a diuretic, such as mannitol, constitute the three bases of treatment. It is far better, however, to avoid the syndrome by prompt treatment of the shock. In the past three years it has become increasingly apparent that crush syndrome and hemoglobinuric nephrosis are not limited to the battlefield.

MECHANISM OF THE VASOCONSTRICTION

Most of you will recall, during the last surge of interest in shock during World War I, that the vasomotor center was one of the chief points of attack. Its failure was held by some to be primary in the cause of shock. Others could demonstrate no failure at any time. To review this phase of the subject would serve no purpose, and so I shall content myself with the statement that there is no cogent evidence to suggest the primacy of failure of the vasomotor center. That it is weakened as shock deepens can hardly be doubted.

At least three possibilities suggest themselves to explain why the blood vessels constrict when blood volume is reduced: (1) physical factors, (2) active neurogenic contraction, and (3) active humoral contraction. The first of these is for the expert in physics and hemodynamics to contend with. I have no means of evaluating this concept. Good investigators take the matter seriously, and so I refer you to them.^{52,58} The second is not easy to register in quantitative terms, but such experiments as there are indicate an important neurogenic element in the vasoconstriction. It was probably first shown most clearly by Seelig and Joseph^{33b} when section of the nerves to a rabbit's ears caused dilatation in the strongly constricted vessels of a rabbit in shock. The explanation of their results is not as simple as it seemed thirty-three years ago; nevertheless, their demonstration carries conviction.

The third possibility, namely the humoral mechanisms, baits the investigator by its apparent simplicity. But, like the country maid, he soon learns. We first suspected the presence of a chemical vasoconstrictor when perfusing plasma, or what seemed to be plasma, of shocked dogs through a rabbit's ear perfused with calcium-free Ringer's solution of plasma.³³ Severe and prolonged constriction resulted. The vasoconstrictor was found in plasma ultrafiltrate as well as in plasma and lymph³⁴ (see Table II). Using a method of fatiguing the vascular muscle so as to obliterate the action of the test drug, it was possible to show that this substance had a similar action regardless of the method by which shock was produced. It did not resemble the usual vasoconstrictors, or even histamine. To our genuine surprise, it appeared in the plasma even after nephrectomy, adrenalectomy, destruction of the nervous system, or renal denervation. The amount of it seemed variable.

TABLE II. CONSTRICTION OF THE VESSELS OF A PERFUSED RABBIT'S EAR RESULTING FROM PLASMA AND ULTRAFILTRATE OF SHOCKED DOGS

	REDUCTION OF FLOW IN MINUTES	PER CENT REDUCTION OF DROP RATE
Control	$\frac{1}{2}$	20
Four hours after release of tourniquets	7	59
Control—bilateral nephrectomy	$2\frac{1}{2}$	54
Two hours after tourniquets	9	60
Control	$1\frac{1}{2}$	25
Two and one-half hours after severe hemorrhage	$6\frac{1}{2}$	48
Control	$\frac{1}{4}$	16
After scalding	16	75
Ultrafiltrate of plasma after scalding	15	56
Control	$1\frac{1}{4}$	34
After intestinal stripping	$6\frac{1}{2}$	85

We have made a much more recent effort, with Robert Taylor and John Reinhard, to learn more about vasopressors or dilators in shocked animals, by cross-transfusion experiments. Two to three days before the experiment, nephrectomy was performed in both animals. The cross transfusion can often be performed without anesthesia, but its use has seemed to make no significant difference in any case. At intervals of about fifteen minutes, test doses of 600 c.c. of blood are crossed, care being taken that the same amount of blood is in transit each way simultaneously. Blood can be transfused back and forth in nephrectomized dogs without affecting the arterial pressure of either animal. But if occluding tourniquets are placed on both hind legs of a nephrectomized donor animal for five hours, and then released, blood from such an animal shows a significant pressor action in the indicator dog, while the latter's blood causes no rise in arterial blood pressure in the donor (Fig. 9). Unfortunately, the story is seldom as simple as this because, commonly, the same type of arterial pressure rise occurs under a variety of conditions unassociated with manifest shock. It seems unlikely, therefore, that this could be the only vasoconstrictor involved in shock.

After several such crosses, no further, or much diminished, responses occur, due, we believe, to exhaustion of the vasopressor substance. If the indicator dog is given enough Dibenamine and Priscol to block the action of adrenalin, cross transfusion before exhaustion of the pressor substance in the donor dog causes marked rise in arterial pressure. But if the dosage is increased sufficiently to block nor-adrenalin, no response to cross transfusion occurs. This observation suggests strongly that the substance from the shocked animals is nor-adrenalin or sympathin-like.

The function of the renal vasopressor system, renin, renin-substrate, and angiotonin (hypertensin) in shock is not clear. Sapirstein, Ogden, and Southard³⁵ first reported the presence of a renin-like substance after hemorrhage. They suggested that it acted as a humoral homeostatic agent. Collins and

Hamilton³⁶ found that an angiotonin-like substance increased in the plasma after hemorrhage, while renin-substrate at first rose, then fell, as the hypotension was continued in both intact and adrenalectomized dogs. It is their view that renin from the animal's own kidneys exhausts the renin-substrate, so depriving the body of a compensatory mechanism.

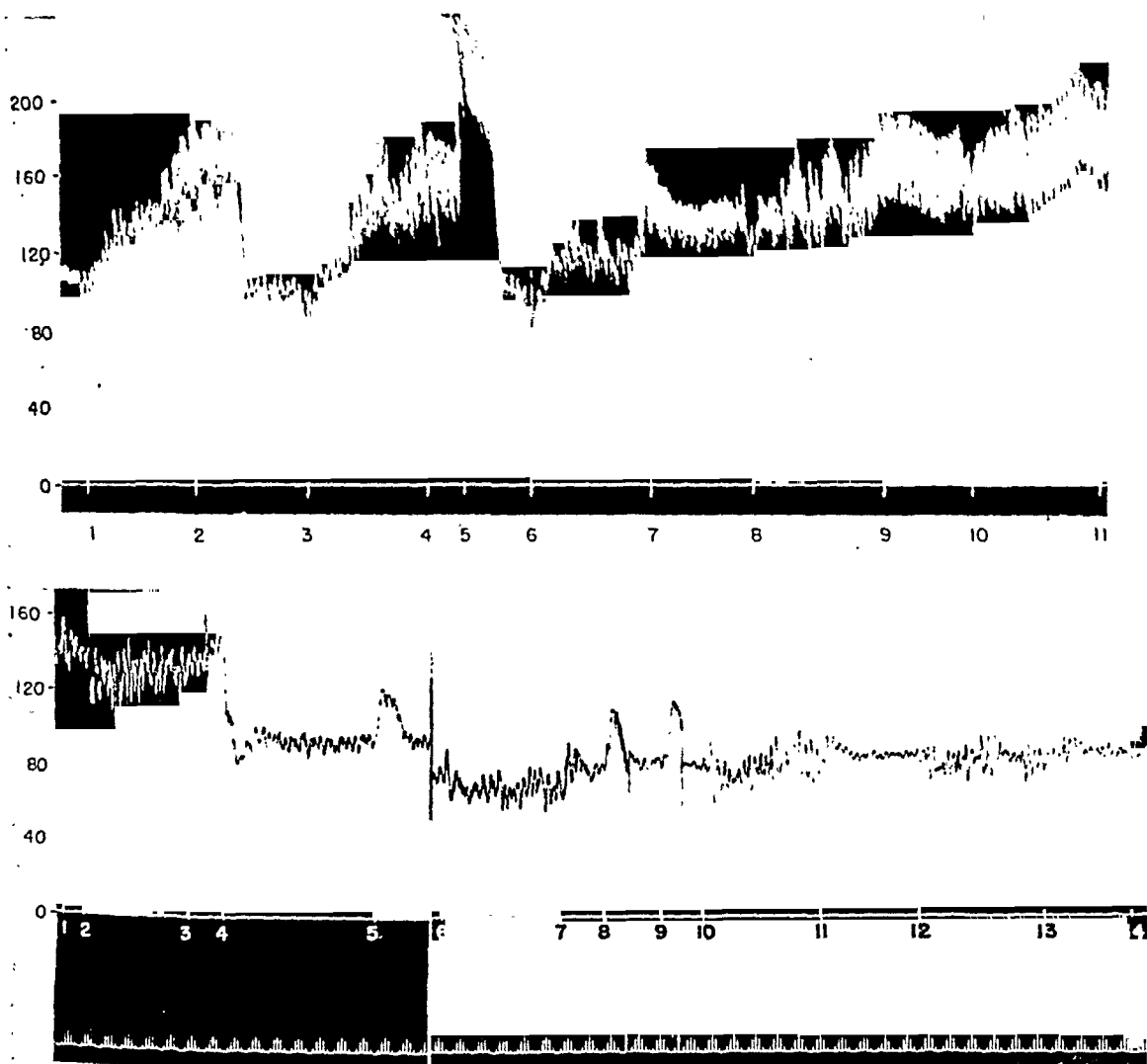


Fig. 9.—Cross transfusion of nephrectomized (two-day) tourniquet dog with a nephrectomized (two-day) dog.

Top graph: Nephrectomized dog. 1-2, Transfusion 600 c.c.; 3-4, same; 5, adrenalin 0.2 c.c.-1:20,000; 6-7, transfusion; 8-9, same; 10-11, same. Time, two hours. *Lower graph:* Nephrectomized tourniquet dog. 1, Adrenalin; 2-3, transfusion; 4, tourniquets removed (had been on five hours); 5, adrenalin; 6-7, transfusion; 8-9, adrenalin; 10-11, transfusion; 12-13, same; 14-15, same.

Further and rather more complete evidence is supplied by Huidobro and Braun-Menéndez.³⁷ They found renin in the systemic blood of dogs after hemorrhage if the kidneys were intact. It was detected after so short a period as four to eleven minutes of profound hypotension. Normally, according to

present crude methods of assay, minimal amounts of renin are secreted by the kidneys.

While it is inferred that the renin vasopressor system is acting as a homeostatic mechanism, there is as yet no proof that this is so. The initial simplicity of the humoral system of which I spoke has vanished beneath even superficial examination!

But there is still another vasoconstrictor, and possibly the most important one of them all. As long as eighty years ago, physiologists were aware that defibrinated blood or serum did not perfuse well through isolated organs because of the vasoconstriction it caused. Somewhat later, and I shall not attempt to document the literature as we have done elsewhere,³⁸ it was recognized that this substance formed when blood clotted and seemed to be associated in some way with the presence of platelets.

Our interest in this factor was aroused on two scores. First, we found pressor and constrictor substances in shocked animals' blood in which the organ of origin seemed to have eluded us. Second, the vascular problem of the spread of hemorrhage in tissue, as, for example, that following infarction of the myocardium or lung, has interested us greatly. Perhaps an ancillary reason is that in assays for pressor substance in the blood of hypertensives, the possible presence of this vasoconstrictor introduced many uncertainties.

Dr. Maurice Rapport, Dr. Arda Green, and I³⁹ decided the only satisfying way of dealing with the problem would be the isolation and attempt to crystallize the factor to see with what we were really dealing. But it soon became apparent that the amounts present in beef, human, or pig serum, were minuscule. However, it was finally possible, by working up small batches of serum at a time, to obtain from about two tons of serum enough material to start work on purification. Success depended chiefly, I think, on the finding that from a butyl alcohol solution the active material could be precipitated by nitrobarbituric acid and on the fact that the rabbit's ear perfusion method admirably served the purpose of quantitative assay. Without this much-maligned method, the isolation would not have been possible.

The substance was finally obtained in thin, rhomboid, yellow platelets, melting at 212 to 214° C. (Fig. 10). A single analysis gave the following ratios: $C_{14} : H_{21} : O_3 : N_5 : H_2SO_4$. I shall not trouble you with the other chemical data as they are not pertinent to our discussion. We have suggested the name serotonin to indicate its source from serum and its activity in causing constriction.

Injection of an aqueous solution of this substance into dogs or cats anesthetized with pentobarbital produced a marked rise in arterial pressure, which was augmented in a chronically sympathectomized animal. The response after pithing was slightly reduced or unchanged (Fig. 11). The rabbit's ileum is sharply contracted by it. The vasoconstrictor activity of the crystalline substance in our perfused rabbit's ear preparation is more than twice that of an equal weight of adrenalin. Constriction is obtained by 0.002 microgram in the ear vessels.

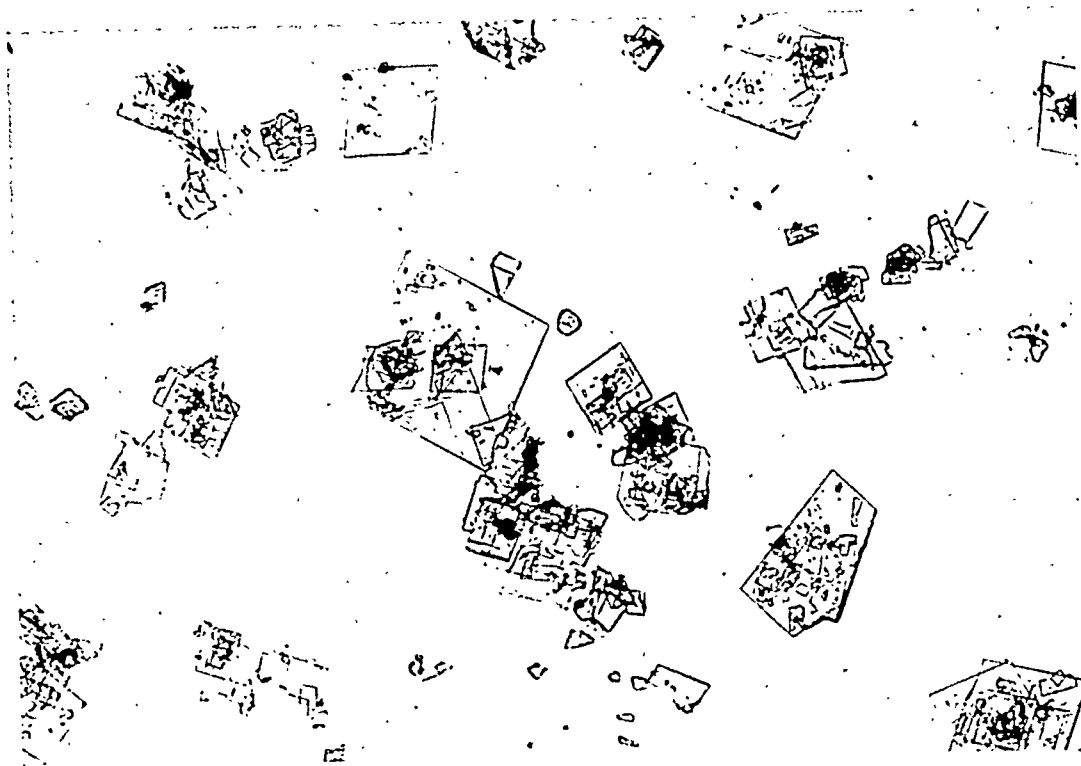


Fig. 10.—Crystals of serotonin.

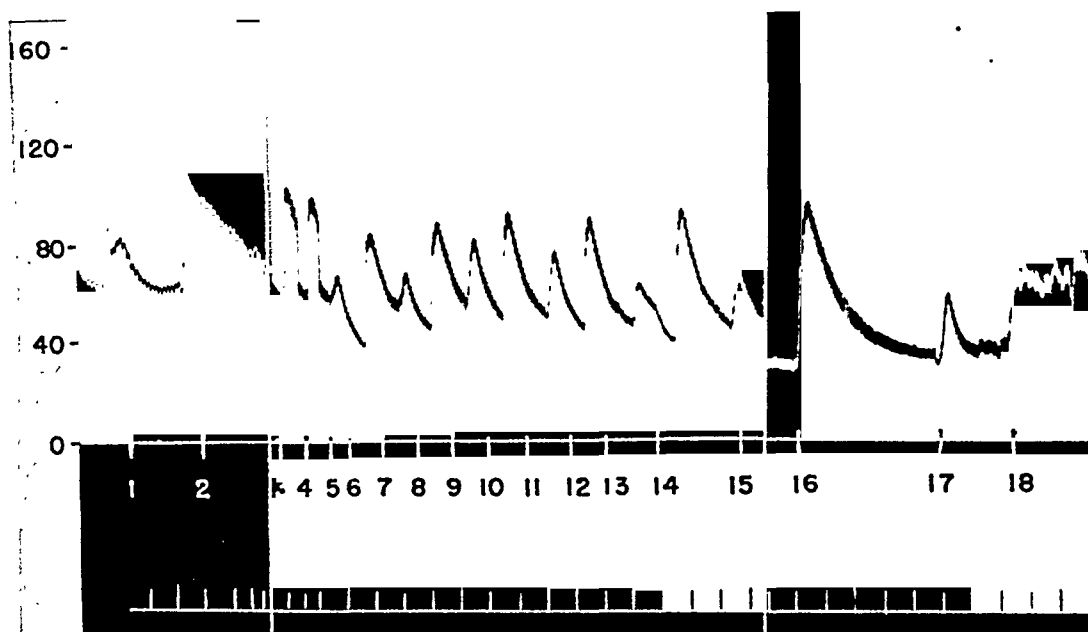


Fig. 11.—Pressor effect of serotonin and adrenalin on intact, pithed, and tetraethyl ammonium-treated, anesthetized cat (No. 472). 1, adrenalin 0.1 c.c. 1:20,000; 2, serotonin 0.1 c.c. 1:4,000, pithed; 3-4, adrenalin; 5, serotonin; 6, adrenalin; 7, serotonin; 8, adrenalin; 9, serotonin; 10, adrenalin; 11, serotonin; 12, adrenalin; 13, tetraethyl ammonium 5 mg. per kilogram; 14, adrenalin; 15, serotonin, four more doses of 5.0 mg. of tetraethyl ammonium; 16, adrenalin; 17, serotonin; 18, renin. (From Rapport, M., Green, A. A., and Page, I. H.: Science 108:329, 1948.³⁹)

Another finding of interest is that lung tissue contains an enzyme which destroys serotonin.⁴⁰ Presumably this is the mechanism by which the vasoconstrictor is removed in perfusion experiments when the blood is passed through the lungs before entering the perfused organ.

I need hardly point out that as yet we know nothing about the part, if any, played by serotonin in shock. But it is tempting to believe that, after trauma and hemorrhage, it either aids in constricting the blood vessels around clots to prevent further hemorrhage, or acts as a constrictor to keep the blood pressure up. But this is pure speculation.

FACTORS INFLUENCING SURVIVAL FROM EXPERIMENTAL SHOCK

We have found no regular correlation between survival after the shock procedure and a number of obvious environmental factors. Thus, weight of the animal, amount of blood required to lower the blood pressure, degree of hydration of the animal, season, initial hemoglobin or hematocrit, initial blood pressure, and other factors showed no significant relationship to survival of the animal.

Since there is good evidence to suggest that as shock progresses, the efficiency of the myocardium becomes impaired, as Wiggers first suggested,⁴¹ and, I believe, as we have substantiated with further evidence,⁴² it seemed of interest to study the effect of ouabain on survival. Ninety-four experiments showed that it did not alter survival, though it seemed to lessen the harmful effects of overtransfusion. The drug with real power to influence the outcome was tetraethyl ammonium chloride. Three years ago, H. C. Wiggers⁴³ presented preliminary evidence that treatment with Dibenamine increased the ability of dogs to withstand hemorrhagic shock. Tetraethyl ammonium ions block ganglionic transmission in all autonomic ganglia. This is followed, as Taylor and I⁴⁴ showed, by marked augmentation of the pressor-depressor responses to a wide variety of vasoactive agents.

When tetraethyl ammonium chloride was given in fifty-one experiments, either before or during the shock procedure, survival was increased in the animals with good prognosis from 85 to 96 per cent, and in those with poor prognosis, from 25 to 44 per cent.

The reason for this improvement seems to us to lie in the important observations made ten years ago by Freeman, Shaffer, Schechter, and Holling.⁴⁵ They showed that in dogs which had had total sympathectomy, blood pressure could be reduced to lower levels and for longer times without producing shock than could be done in normal dogs. But the former animals were unable to tolerate as large hemorrhages as the latter. The difference in reaction was correlated with the peripheral blood flow. In normal dogs, as the arterial pressure was reduced by hemorrhage to 70 mm. Hg, blood flow was reduced below 2.0 c.c. per minute, while in the sympathectomized animal it was above 2.0 cubic centimeters. The preferential treatment of blood supply to vital centers is lost in the sympathectomized animal, but as long as these centers receive sufficient blood supply, all the tissues of the body probably receive an adequate

amount of blood, and shock is prevented. Much the same mechanism seems to be involved in the experiments of Phemister, Eichelberger, and Lacstar,⁶⁰ in which they show that section of the spinal cord at C₈ makes the dogs more resistant to shock than equally low blood pressure elicited by hemorrhage or local fluid loss.

In experiments with Dr. John Reinhard and Dr. Otto Glasser, we found⁶¹ that section of the cord at C₆, several days before the hemorrhage, produced a preparation not unlike the tetraethyl ammonium chloride-treated animal. Somewhat less blood needed to be removed (3.9 per cent, as compared with 5.1 per cent for normal animals) to reach the hypotensive levels, and the animals withstood the procedure with less apparent injury than normal dogs. Indeed, it was possible to subject two of the animals to a repetition of the procedure three days after the first experiment (Fig. 12). Even though only three-fourths of the blood was returned during each retransfusion, they both survived. The animals were, as was to be expected, hypersensitive to vaso-active chemical stimuli. It seems possible, if unproved, that this, along with the better perfusion of tissues, confers the heightened ability to withstand shock.

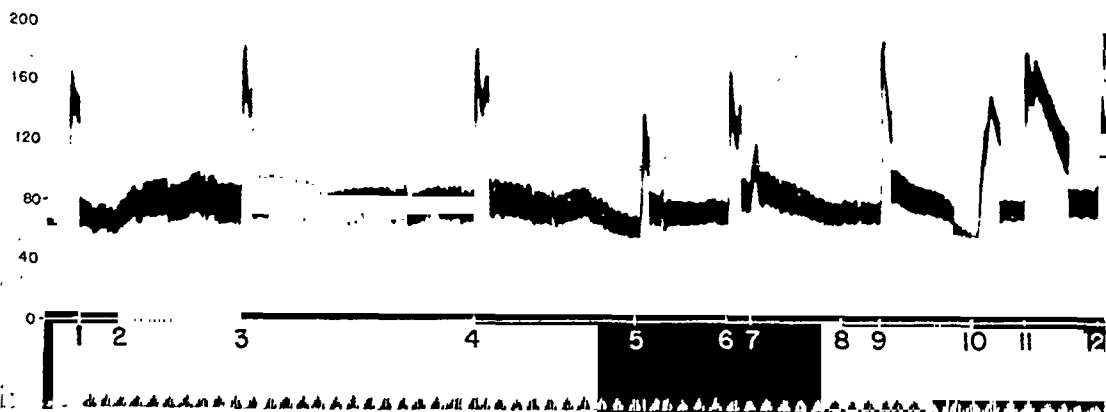


Fig. 12.—The uptake of saline from reservoir connected to the femoral artery, and adrenalin response in an unanesthetized dog (weight 7.8 kilograms) whose spinal cord had been sectioned at C₆ one day before. Fluid intake at top represents 1.0 liter. Time in minutes. Adrenalin 0.2 c.c. 1:20,000. 1, Adrenalin; 2, saline reservoir opened at 60 mm. Hg pressure; 3-6, adrenalin; 7-8, tetraethyl ammonium chloride 5 mg. per kilogram; 9-12, adrenalin.

In view of these results, it became imperative to examine the effects of removal of other organs. Experimental results are at variance, and opinion, as well, is greatly divided as to the part the kidneys play in the mechanism of shock. Animals subjected to the shock procedure at various times after nephrectomy withstood it apparently neither better nor worse than did normal animals. We were unable to detect a difference. In some anesthesia was used and in others it was not used. The same result was obtained by Bobb⁵⁵ in nephrectomized and normal dogs subjected to compression of the hind legs

for six hours. Further, Hechter, Bergman, and Prinzmetal⁵⁶ could find no influence of the renal pressor system on either mortality or survival time in mice subjected to burn shock.

Next the liver was removed in our dogs. The animals usually were in excellent condition for periods up to ten hours or more after the operation. Most of them lost a significant amount of blood by diapedesis through the peritoneum. To our great surprise, these animals withstood the shock procedure quite as well as did normal dogs. The blood pressure curves are superimposable. As in the case of the animals with cord section, somewhat less blood is shed to produce comparable blood pressure reduction. In other experiments both the kidneys and the liver were removed, but still without change in the response to the shock procedure.

We recognize that the meaning of these experiments is difficult to determine. The fact that with the exclusion of the liver a large vascular bed is removed, along with a not inconsiderable amount of blood, may mean a change in the entire circulation. With many reservations in mind, about the most that one dare say is that it is altogether surprising that so little difference was observed in the immediate response to hemorrhage. Especially in the case of hepatectomy, the unavoidable loss of blood into the peritoneum and the removal of such a large blood-containing organ militate against the animals' ability to withstand hemorrhage, yet we detected no difference. For these and other reasons, it seems wise to record the observations, which are in sufficient number to be indisputable, but to leave interpretation for the future.

THE REACTIVITY OF BLOOD VESSELS

It is not an easy matter to decide how important are changes in the responsiveness of blood vessels to stimuli during the course of shock. We have seen that substances which affect the vasoconstrictor activity of the nerves, such as tetraethyl ammonium chloride and Dibenamine, affect survival after hemorrhage. The former increases vascular responsiveness to agents like adrenalin, while the latter decreases it. Thus, we might conclude that it makes little difference what the drug does to the reactivity of the vessels, except for the caution that the action of these drugs is exceedingly complicated. Evidence of this sort needs be accepted with wide reservation.

What, then, is the evidence favoring the view that vascular reactivity is important in shock? Six years ago we observed that the pressor response to angiotonin and adrenalin fell progressively either after injury to the central nervous system or after shock from hemorrhage or scalding (Fig. 13). In the case of hemorrhagic shock, if the response returned to full vigor after retransfusion, the likelihood of survival was materially increased.

The heart participated in the loss of responsiveness, as demonstrated by the lack of response to adrenalin when its contractions were studied in a cardiometer.⁴⁶ Not only does the blood pressure show far less rise after a dose of adrenalin, but the heart does not exhibit the usual sharp diminution in size

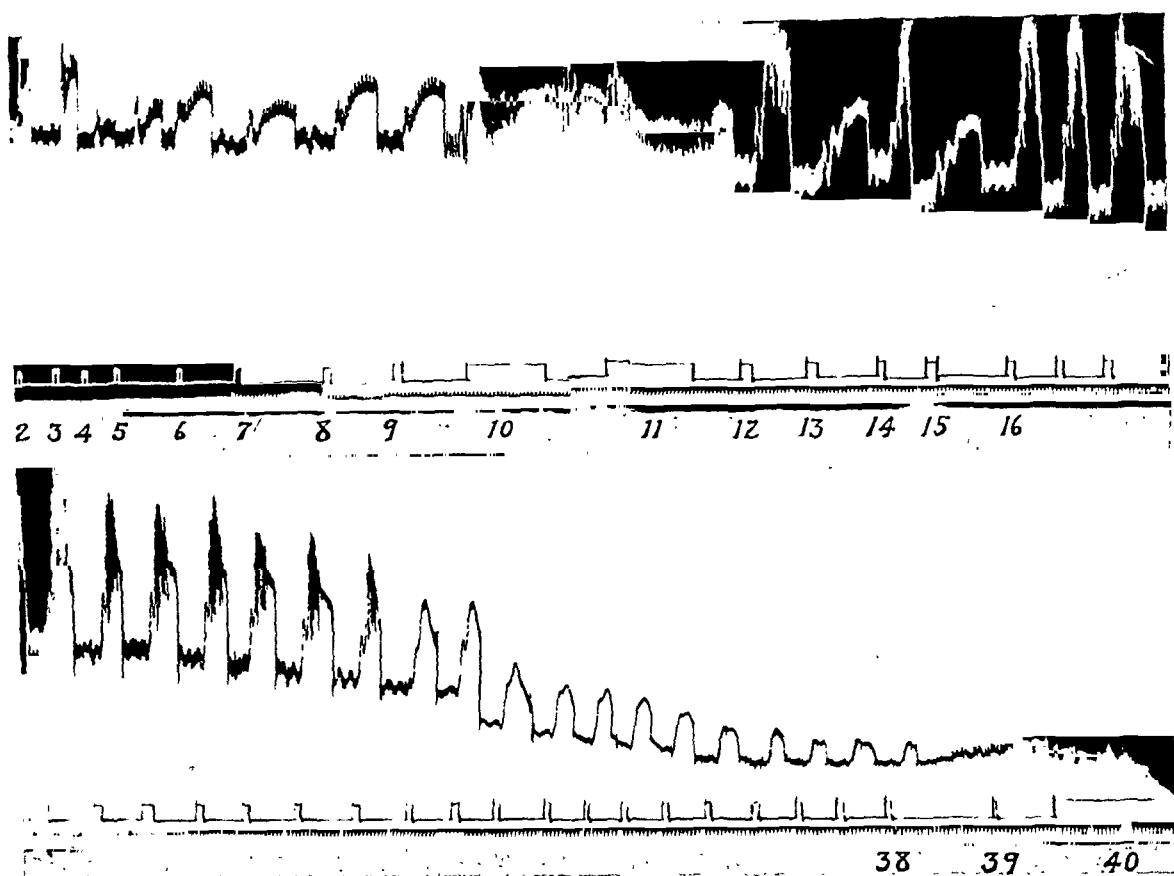


Fig. 13.—The effect of scalding on the vascular response of a dog to adrenalin and Tyramine. 2-3, Adrenalin, 0.3 c.c. 1:10,000; 4, Tyramine 1.0 mg.; 5-9, Tyramine 2.0 mg.; 10-11, scalded; 12, adrenalin; 13, Tyramine; 14, adrenalin; 15, Tyramine; 16-38, adrenalin; 39, Tyramine; 40, plasma infusion. (From Page, I. H.: *Am. J. Physiol.* **142**:366, 1944.¹⁴)

(Fig. 14). Thus if our experiments have sampled fairly, the entire musculature of the vascular system appears to participate in this gradual loss of responsiveness as shock develops.

Probably less significant is the observation that administration of either the antihistaminic, Benadryl, or the metal-containing enzyme depressant, BAL, in sufficient doses, reduces or altogether blocks the action of a variety of stimulating drugs. The arterial pressure often may be maintained at normal levels in such animals for thirty minutes or more (Fig. 15), but sudden and fatal fall in blood pressure may occur at any time without warning. Much the same phenomenon has been observed in shocked animals.

Thus, while it appears that blood vessels and heart, able to respond actively to chemical stimulation, aid in the fight for survival against shock, maintained responsiveness is only one of many factors.

Just what significance to attribute to the work initiated by Chambers and Zweifach,⁴⁷ and carried on by Shorr and Zweifach, concerning the appearance in the blood of vasoexcitor and depressor materials, it is, in my opinion, pre-

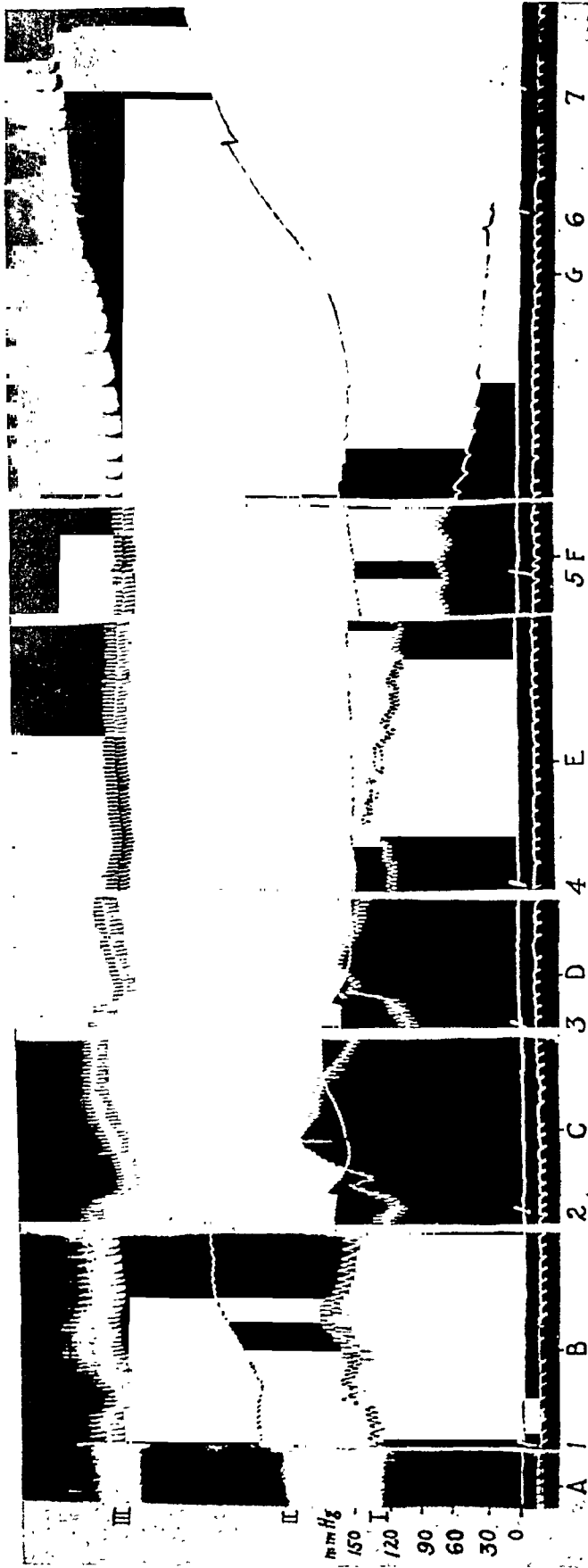


Fig. 14.—*I*, Arterial pressure measured in carotid artery by a mercury manometer. *II*, Intrathoracic venous pressure measured by a water manometer. *III*, Cardiac output measured by cardiometer. Cardiometer used at normal intrathoracic pressure. Lower border of tracing is the systolic volume; upper border is the diastolic volume.

Section *A*: Control period; drum moving slowly. Section *B*: Control period; drum moving fast. *1*, 0.4 c.c. 1:10,000 adrenalin. Section *C*: one hour and ten minutes after abdomen, back, and hind legs were burned. *2*, 0.4 c.c. 1:10,000 adrenalin. Section *D*: Fifty minutes elapsed between *C* and *D*. *3*, 0.4 c.c. 1:10,000 adrenalin. Section *E*: Three hours after *D*. *4*, 0.4 c.c. 1:10,000 adrenalin. Section *F*: Ten minutes after *E*. *5*, 0.5 c.c. 1:10,000 adrenalin. Section *G*: Fifteen minutes after *F*. *6*, 0.4 c.c. 1:10,000 adrenalin. *7*, 0.4 c.c. 1:10,000 adrenalin. (From Page, I. H.: *Am. J. Physiol.* **142**:366, 1944.¹⁴)

mature to judge. It is an interesting and imaginative investigation, but so far lacks cogent proof of its actual participation in the mechanism of shock.

It has been of some interest to follow the change in vascular capacity for fluid, such as saline or blood, during changes in vascular responsiveness. The pressure in the reservoir is set at 100 to 120 mm. Hg, the connection with the femoral artery opened, and the output or intake registered by the movements of the reservoir. Perhaps the most common picture after scalding is a rapid uptake of fluid from the reservoir, followed by slowing and even some output of blood from the animal to the reservoir. As vascular reactivity fails, the uptake increases rapidly, until during the last thirty minutes of life, the uptake is great. A small dog may take up 2.0 liters or more in this short span. The changing balance of fluid in the reservoir and in the vascular system proved quite a reliable guide to prognosis in these experiments.

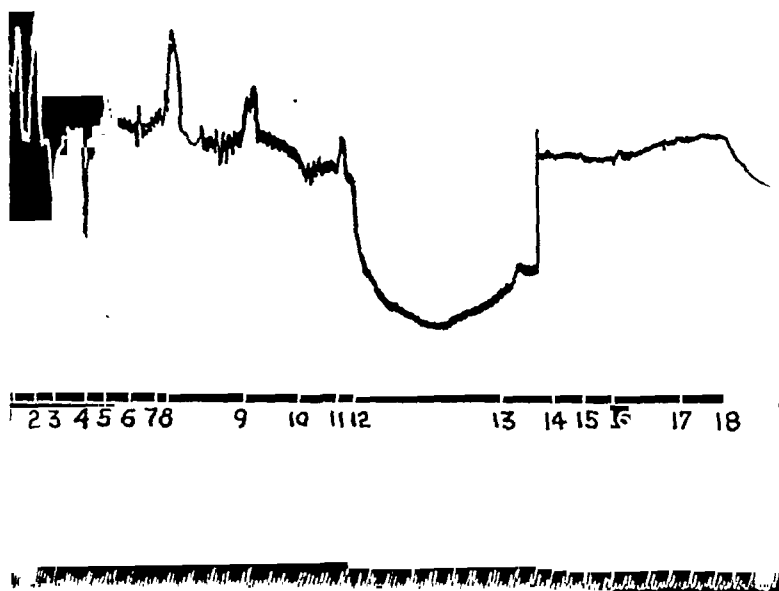


Fig. 15.—Refractoriness produced by large doses of BAL. 1-2, Adrenalin; 3-4, histamine; 5, barium chloride; 6-7, emulsion of BAL intraperitoneally; 8, adrenalin; 9, pure BAL, 1 c.c. intraperitoneally; 10, adrenalin; 11, 0.5 c.c. BAL; 12-13, adrenalin; 14, histamine; 15-17, adrenalin; 18, barium chloride.

The response of supposedly normal dogs to equilibration of their circulation with a pressure reservoir is interesting and often unexpected. The usual animal may take up from 500 to 1,000 c.c. in thirty minutes, or none at all, from the reservoir if the pressure is set about 20 mm. Hg above its own average. Then uptake slows, and for a period from two to twelve hours either some blood may be forced into the reservoir or the uptake amount to some 200 c.c. per hour. On the other hand, some animals immediately take up a liter or more, and the adrenalin response and blood pressure falls as soon as the connection with the reservoir is closed. The uptake of fluid then increases rapidly, reaching 500 c.c. or more in ten minutes. Circulation fails quickly.

The reason for the differences among these "normal" dogs is not known to us, striking as the differences be (Fig. 16).

Certainly vascular responsiveness is not the only, if, indeed, the most important factor in the changed relationship between intake and output of fluid. When adequate fluid is given by this method, responsiveness is maintained in these animals long after it is lost in animals receiving no fluids. But maintenance of some degree of responsiveness does not insure survival of the animals. It only weighs in its favor, just as lack of rapid uptake of fluid by the animal similarly weighs against survival.

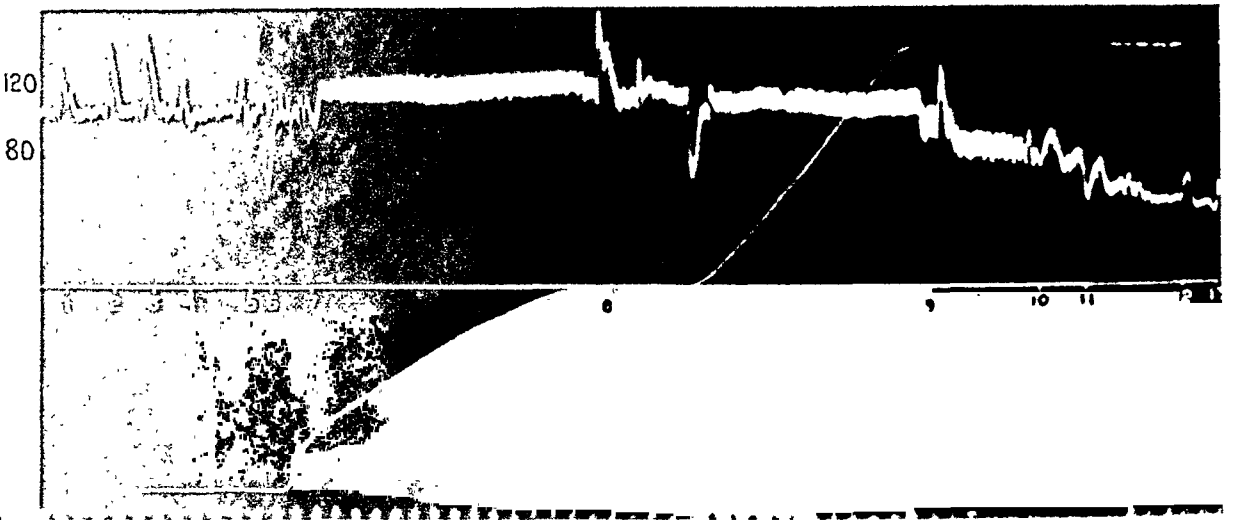


Fig. 16.—Rapid uptake of fluid and early circulatory failure in a supposedly normal dog. 1-3, Adrenalin; 4-5, nicotine; 6, histamine; 7, reservoir opened at 120 mm. Hg; 8, adrenalin; 9, nicotine; 10, histamine; 11, adrenalin; 12, nicotine; 13, adrenalin; 400 c.c. in first ten minutes and 600 c.c. in next ten minutes.

INTRA-ARTERIAL TRANSFUSION

There is one factor in the treatment of shock on which all will agree: blood volume must be restored to normal in as short a time as possible. In the terminal phase, every minute counts. Since blood has become easily available, the remaining problem is how to give it most effectively.

The principle of giving blood by artery extends well back into the annals of physiology, and was used in a few patients by Halstead and George Crile. But the technical difficulties were not solved, nor were the reasons for its use in this fashion understood, and so the method was discarded. Early in the war, Colonel Sam Seeley, U. S. A., suggested to us that the problem be investigated, and thus began our work on the subject in 1941, first with Dr. K. G. Kohlstaedt^{13,46} and later with Dr. Otto Glasser.⁴⁵

Among the reasons for giving blood by artery instead of by vein are the following:

1. Blood pressure is restored to normal levels within a few minutes, and the pressure is controllable.

2. Blood volume deficits are automatically corrected. That amount of blood will be taken into the circulation which is required to fill it at a given arterial pressure.

3. When the heart and respiration have failed, blood given into an artery often brings about resuscitation.

Other reasons will be discussed later. The important thing to remember is that a secondary heart provides pressure to fill the vascular tree and maintain pressure in it.

The apparatus required is simple. For animals, Fig. 2 gives an idea of how it is set up. For human beings, it is much simpler, consisting merely of a pressure reservoir with a manometer connected to the femoral or radial artery (Fig. 17). If the need is urgent, an 18 gauge needle may be inserted, point-

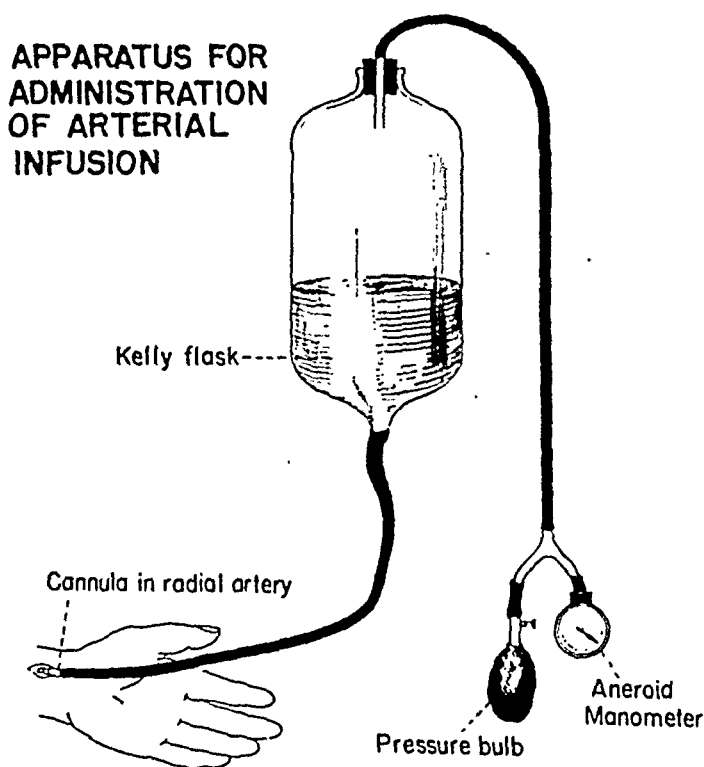


Fig. 17.—Simple apparatus for emergency arterial transfusion.

ing toward the heart, or a glass cannula may be tied in if time permits. Heparin solution is used to prevent coagulation in the cannula and tubing, but the blood itself in the reservoir may be citrated unless very large amounts are to be given, when the use of heparin becomes more desirable. Murphy drips, or any sort of contrivance which might trap air, are carefully to be avoided as there is always danger of air embolism when blood enters the arterial circulation at a fast rate. I need not trouble you with the details of the procedure which I have described elsewhere.⁵⁹ Dr. Donald Hale of the Department of Anesthesiology of the Cleveland Clinic has now had a wide experience in the use

of this method on patients. Suffice it to say that the procedure is extremely simple, the apparatus is mobile, and nothing that is not ordinary hospital equipment need be used. But if the method is to be used, assemblies of the apparatus must be ready on every floor of a hospital for emergencies such as exsanguination and resuscitation.

In practice, if the blood pressure is 30 mm. Hg or less, the pressure in the reservoir should be set 20 mm. higher, and blood allowed to flow in. The pressure is then raised in increments of 20 mm. until the systemic pressure is 100 mm. of mercury. It is seldom advisable to raise the pressure higher, as irregularities of the heartbeat and signs of embarrassment of the circulation often develop at higher pressures. It may be desirable to leave the patient's artery open to the reservoir at this pressure for a time, until it is reasonably sure that the pressure will hold.

A fact of interest that we observed some time ago¹³ was that given by artery, little more than half the amount of blood was required to restore arterial pressure than when blood was given by vein. Perhaps the important



Fig. 18.—Intra-arterial infusion of Skiodan into the femoral artery of a dog deeply in shock, with extreme hypotension. Note that the kidneys fill first.

thing to remember is that in case of emergency it makes little difference what fluid is administered to keep the circulation going until the more suitable blood is available. To wait for blood to be brought from the blood bank and warmed to body temperature is to lose a life.

There are a number of interesting observations that have been made during the course of this work. The one that interested me most was that at low systemic pressures blood flows retrograde up the aorta and perfuses the coronary and medullary vessels. We had noticed on several occasions that, very shortly after the infusion was started in patients who had ceased breathing, a deep breath was taken. With the help of Dr. Robert Hughes of the Cleveland Clinic, we took serial x-ray photographs of a dog deeply in shock while it was receiving an arterial transfusion of radiopaque material. They showed that the kidneys filled first, and immediately thereafter the coronary and the medullary circulations (Figs. 18 and 19). One could hardly wish for finer photographs of the coronary vessels!



Fig. 19.—Same animal as in Fig. 18 a few seconds later. The coronary and medullary vessels have now filled.

This seems to explain why we were able to resuscitate, with a combination of intra-arterial infusion of blood and adrenalin and artificial respiration, animals in which circulation and respiration had ceased.

Thirty-nine experiments on dogs were performed by Glasser in which, after the usual hemorrhagic shock procedure, more blood was withdrawn until the respiration and heart stopped, as indicated by electrocardiographic and pneumographic records.

Respiration stopped first, and was started artificially in from two to eight minutes. When the heart had stopped for about two minutes, treatment by rapid intra-arterial transfusion, along with adrenalin and ouabain, was begun. Enough heparin had entered the animal's circulation to reduce the possibility of coagulation of the blood.

Eighty-four per cent of the animals could be resuscitated; 51 per cent lived for an average of ten hours, and 33 per cent survived, apparently unharmed, indefinitely. An example of one of these experiments is given in Fig. 20. Obviously, an intravenous transfusion would not have been useful.

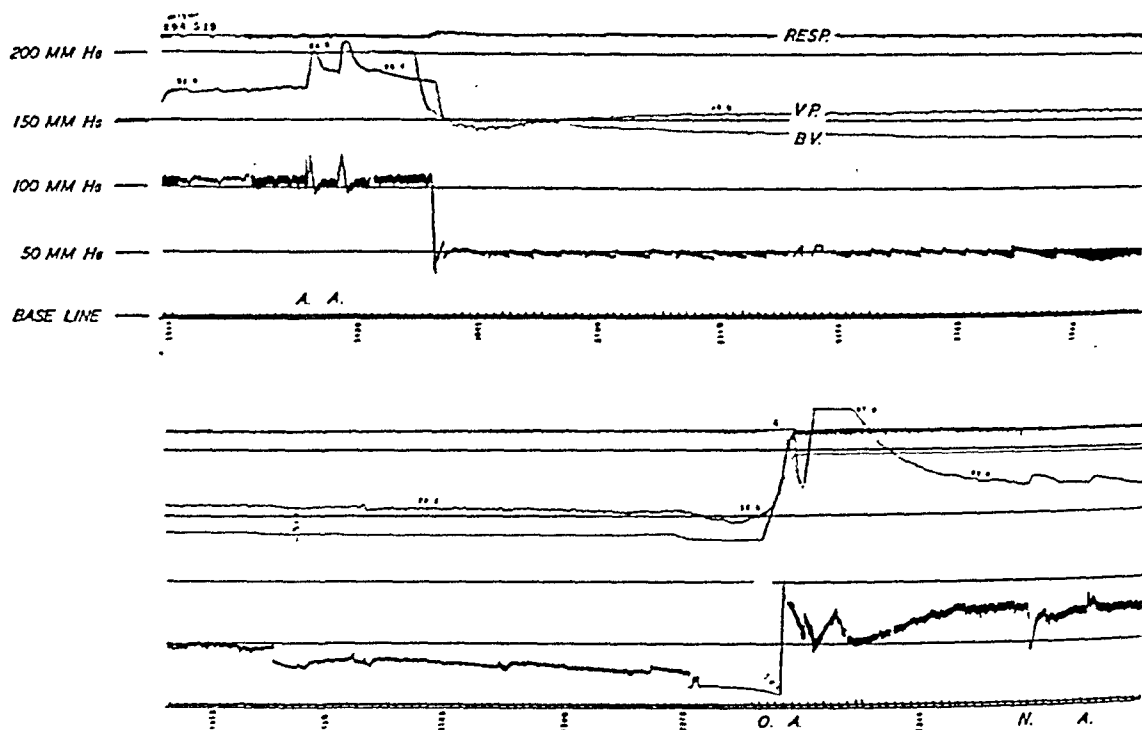


Fig. 20.—Resuscitation of a dog which had been subjected to the shock procedure, and then bled until heart (two and one-half minutes) and respiration (four minutes) stopped. Arterial transfusion plus ouabain and adrenalin given at O.A. The animal survived.

Also of interest is the fact that it was possible, in patients, to locate bleeding vessels in the abdomen which no longer bled and hence were lost to sight when the pressure had fallen to a very low level. When the pressure was raised for a minute or so, blood spurted from the broken vessel, allowing its ligation.⁴⁹ On a number of occasions, this maneuver has proved itself useful (Fig. 21).

Dr. James Gardner⁵⁰ has used the procedure in some fifty patients to reduce the risk of severe blood loss during cranial operations. With Dr. Donald Hale he has transferred about 2.0 liters of blood to reservoir bottles and re-

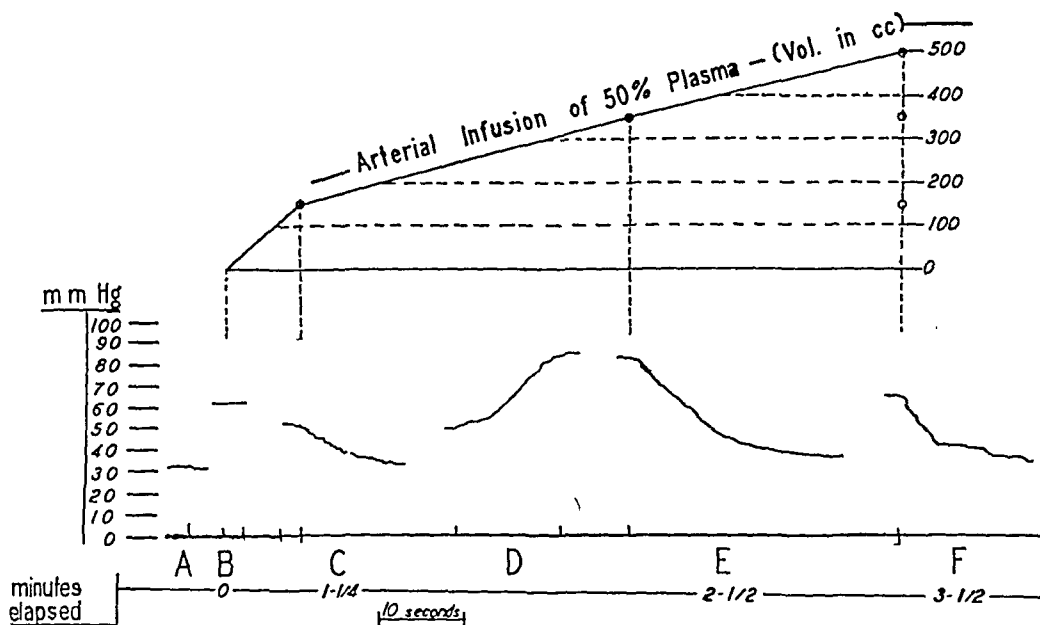


Fig. 21.—Example of the effect of intra-arterial infusion in a patient in deep shock with undiagnosed abdominal bleeding. Arterial pressures are recorded on a kymograph. A, Initial pressure; B, pressure during intra-arterial infusion; C, infusion was discontinued and pressure fell off rapidly; D, reinstituted; E, infusion stopped; F, same sequence repeated. Clearly blood was leaking rapidly from the vascular tree. (Kohlstaedt and Page.)

duced the blood pressure to 80 or 90 (Fig. 22). Their experience shows that, at this level, bleeding in the brain is greatly reduced and operation materially facilitated. This is especially true with such tumors as olfactory groove meningiomas, where the pedicle is not reached until the bulk of the tumor is already cut away. Bleeding may be severe and dangerous. The operating time may be reduced to less than half and blood loss to insignificance. Before the cavity is closed, the patient again receives all but 500 c.c. of his blood; this may be given later, intravenously, if needed.

Dr. Harold Harris⁵¹ has also used the procedure for induced hypotension in some fifty cases to lessen hemorrhage during a critical stage in the fenestration operation. He believes his results more secure when at one point in the operation blood is removed and replaced as soon as the dangers of hemorrhage are past.

In dogs, we have avoided many of the great and sometimes disastrous falls in blood pressure when operations are being performed on the aorta. By judicious removal of blood when the aorta is being closed, and its rapid readmission when the aorta is being opened, significant changes in arterial pressure may be almost wholly avoided. Kay⁵² has described the use of this procedure to maintain life while suturing stab wounds in the heart.

It must be evident to any thoughtful person that arterial transfusion has specific and limited application. It obviously does not replace intravenous transfusion except under special conditions. Nor can its use for induced hypotension in surgery be profitable except where there is definite indication for the procedure, and where the anesthetist has had experience in its use. On the

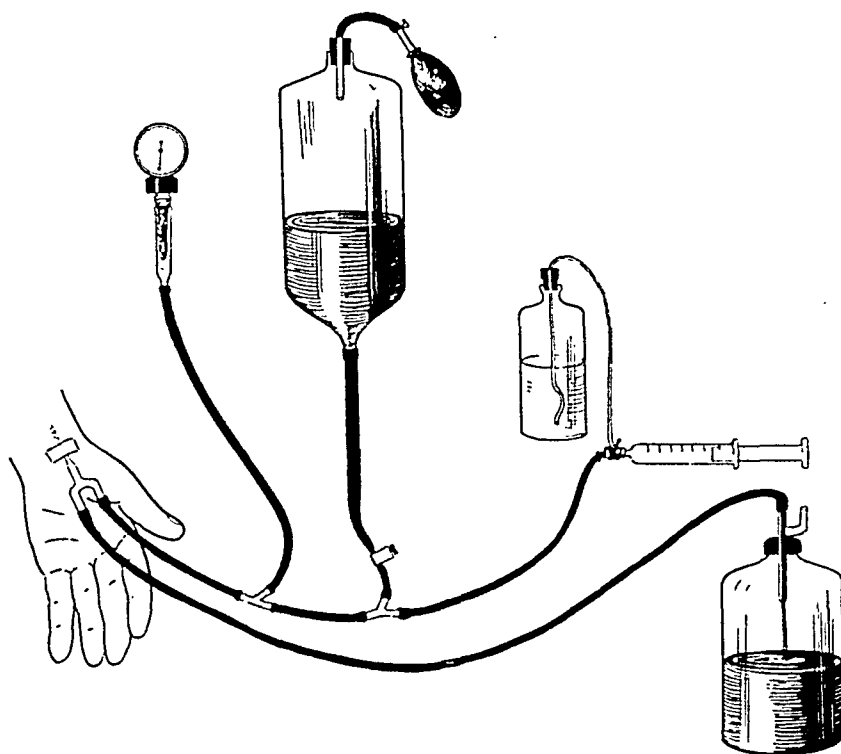


Fig. 22.—Apparatus used for induced hypotension in patients. The syringe and small bottle contain heparin solution to prevent coagulation in the tubing.

other hand, in certain circumstances, such as deep shock, resuscitation, exsanguination, location of bleeding vessels, and operations in which blood loss may be serious, it may prove invaluable. If it does nothing else but call the attention of the physician to the necessity of speed in the treatment of shock, it will have served a real purpose.

REFERENCES

1. Gesell, R.: Studies on the Submaxillary Gland. III. Some Factors Controlling the Volume-Flow of Blood, *Am. J. Physiol.* 47:438, 1918.
2. Page, I. H., Taylor, R. D., and Kohlstaedt, K. G.: A Case of Extreme Hypotension Following Acute Arsenic Poisoning With Adequate Blood Supply to the Tissues, *Am. J. Med.* 205:730, 1943.
3. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, 1940, The C. V. Mosby Company.
4. Parsons, E., and Phemister, D. B.: Hemorrhage and "Shock" in Traumatized Limbs, an Experimental Study, *Surg., Gynec. & Obst.* 51:196, 1930.
5. Gregersen, M. I.: Symposium on Physiological Contributions to War Problems; Physiological Contributions to Problem of Shock, *Federation Proc.* 5:354, 1946.
6. Gibson, J. G., Seligman, A. M., Peacock, W. C., Aub, J. C., Fine, J., and Evans, R. D.: Distribution of Red Cells and Plasma in Large and Minute Vessels of Normal Dogs Determined by Radioactive Isotopes of Iron and Iodine, *J. Clin. Investigation*, 25:848, 1946.

7. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I., and Richards, D. W., Jr.: Studies of Circulation in Clinical Shock, *Surgery* 13:964, 1943.
8. Wilhelmi, A. E.: Metabolic Aspects of Shock, *Ann. Rev. Physiol.* 10:259, 1948.
9. McMichael, J.: Clinical Aspects of Shock, *J. A. M. A.* 124:274, 1944.
10. Howarth, S., and Sharpey-Schafer, E. P.: Low Blood Pressure Phases Following Haemorrhage, *Lancet* 1:18, 1947.
11. Glasser, O., and Page, I. H.: Experimental Hemorrhagic Shock; A Study of Its Production and Treatment, *Am. J. Physiol.* 151:297, 1948.
12. Wiggers, C. J., and Werle, J. M.: Explanation of Method for Standardizing Hemorrhagic Shock, *Proc. Soc. Exper. Biol. & Med.* 49:604, 1942.
13. Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment of Intrarterial and Intravenous Infusion of Blood, *Arch. Surg.* 47:178, 1943.
14. Page, I. H.: Cardiovascular Changes Resulting From Severe Scalds, *Am. J. Physiol.* 142:366, 1944.
15. Page, I. H., and Abell, R. G.: The State of the Vessels of the Mesentery in Shock Produced by Constricting the Limbs and the Behavior of the Vessels Following Hemorrhage, *J. Exper. Med.* 77:215, 1943.
16. Page, I. H., and Abell, R. G.: Effects of Acute Hemorrhage and of Subsequent Infusion Upon the Blood Vessels and Blood Flow as Seen in the Mesenteries of Anesthetized Dogs, *Am. J. Physiol.* 143:182, 1945.
17. Abell, R. G., and Page, I. H.: A Study of the Smaller Blood Vessels in Burned Dogs and Cats, *Surg., Gynec. & Obst.* 77:348, 1943.
18. Wiggers, C. J., Opdyke, D. F., and Johnson, J. R.: Portal Pressure Gradients Under Experimental Conditions, Including Hemorrhagic Shock, *Am. J. Physiol.* 146:192, 1946.
19. Selkurt, E. E., Alexander, R. S., and Patterson, M. B.: Role of Mesenteric Circulation in Irreversibility of Hemorrhagic Shock, *Am. J. Physiol.* 149:732, 1947.
20. Opdyke, D. F., and Foreman, R. C.: A Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock, *Am. J. Physiol.* 148:726, 1947.
21. Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs, *J. Exper. Med.* 78:205, 1943.
22. Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Jr., Archibald, R. M., and Van Slyke, D. D.: Effect of Acute Hemorrhage and Traumatic Shock on Renal Function of Dogs, *Am. J. Physiol.* 145:314, 1946.
23. Selkurt, E. E.: Renal Blood Flow and Renal Clearance During Hemorrhagic Shock, *Am. J. Physiol.* 145:699, 1946.
24. Lauson, H. D., Bradley, S. E., and Cournand, A.: The Renal Circulation in Shock, *J. Clin. Investigation* 23:381, 1944.
25. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Immediate Effects on Renal Function of the Onset of Shock Due to Partially Occluding Limb Tourniquets, *Ann. Surg.* 118:871, 1943.
26. Bywaters, E. G. L., and Beall, D.: Crush Injuries With Impairment of Renal Function, *Brit. M. J.* 1:427, 1941.
27. Corcoran, A. C., and Page, I. H.: Post-traumatic Renal Injury—Summary of Experimental Observations, *Arch. Surg.* 51:93, 1945.
28. Corcoran, A. C., and Page, I. H.: Crush Syndrome, Post-traumatic Anuria—Observations on Genesis and Treatment, *J. A. M. A.* 134:436, 1947.
29. Maegraith, B. G., Havard, R. F., and Parsons, D. S.: Renal Syndrome of Wide Distribution Induced Possibly by Renal Anoxia, *Lancet* 2:293, 1945.
30. Lucké, B.: Lower Nephron Nephrosis: The Renal Lesions of the Crush Syndrome, of Burns, Transfusions and Other Conditions Affecting the Lower Segment of the Nephron, *The Military Surgeon* 99:371, 1946.
31. Mallory, T. B.: Hemoglobinuric Nephrosis in Traumatic Shock, *Am. J. Clin. Path.* 17:427, 1947.
32. Little, J. M., Green, H. D., and Hawkins, J. E., Jr.: Evidence From Crosstransfusion Experiments That Diminished Urine Flow Accompanying Ischemic Compression Shock Is not Due to Humoral Factors, *Am. J. Physiol.* 151:554, 1947.
33. (a) Page, I. H.: The Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage and Burns, *Am. J. Physiol.* 139:386, 1943.
 (b) Seelig, M. G., and Joseph, D. R.: On the Condition of the Vaso-Constrictor Center During the Development of Shock, *J. Lab. & Clin. Med.* 1:283, 1915.

34. Alrich, E. M.: Studies on Burns. II. Observations on a Vasoconstrictor Substance in Lymph From a Burned Area, *Surgery* 15:908, 1944.
35. Sapirstein, L. A., Ogden, E., and Southard, F. D., Jr.: Renin-like Substance in Blood After Hemorrhage, *Proc. Soc. Exper. Biol. & Med.* 48:505, 1941.
36. Collins, D. A., and Hamilton, A. S.: Changes in the Renin-Angiotonin System in Hemorrhagic Shock, *Am. J. Physiol.* 140:499, 1943.
37. Huidobro, F., and Braun-Menendez, E.: Secretion of Renin by Intact Kidney, *Am. J. Physiol.* 137:47, 1942.
38. Rapport, M., Green, A. A., and Page, I. H.: Serum Vasoconstrictor. IV. Isolation and Characterization, *J. Biol. Chem.* 176:1243, 1948.
39. Rapport, M., Green, A. A., and Page, I. H.: Crystalline Serotonin, *Science* 108:329, 1948.
40. Rapport, M., Green, A. A., and Page, I. H.: Partial Purification of the Vasoconstrictor in Beef Serum, *J. Biol. Chem.* 174:735, 1948.
41. Wiggers, C. J.: Myocardial Depression in Shock; Survey of Cardiodynamic Studies, *AM. HEART J.* 33:633, 1947.
42. Page, I. H.: Participation of the Heart in Shock, *Mod. Concepts Cardiovas. Dis.* 16:1 *Am. Heart Assoc.*, New York, 1947.
43. Wiggers, H. C., Ingraham, R. C., Roemhild, F., and Goldberg, H.: Vasoconstriction and the Development of Irreversible Hemorrhagic Shock, *Am. J. Physiol.* 153:511, 1948.
44. Page, I. H., and Taylor, R. D.: Mechanism of Renin Tachyphylaxis—Restoration of Responsiveness by Tetraethyl Ammonium Ion, *Science* 105:622, 1947.
45. Freeman, N. E., Shaffer, S. A., Schechter, A. E., and Holling, H. E.: Effect of Total Sympathectomy on Occurrence of Shock From Hemorrhage, *J. Clin. Investigation* 17:359, 1938.
46. Kohlstaedt, K. G., and Page, I. H.: Terminal Hemorrhagic Shock; Circulatory Dynamics, Recognition and Treatment, *Surgery* 16:430, 1944.
47. Chambers, R., and Zweifach, B. W.: Blood-borne Vasotropic Substances in Experimental Shock, *Am. J. Physiol.* 150:239, 1947.
48. Glasser, O., and Page, I. H.: Experimental Hemorrhagic Shock; A Study of Its Production and Treatment, *Am. J. Physiol.* 154:297, 1948.
49. Page, I. H.: Treatment of Shock by Intra-arterial Infusion, *Bull. U. S. Army M. Dept.* 7:366, 1947.
50. Gardner, W. J.: The Control of Bleeding During Operation of Induced Hypotension, *J. A. M. A.* 132:572, 1946.
51. Harris, H. E., and Hale, D. E.: Induced Hypotension in the Control of Bleeding During the Fenestration Operation, *Tr. Am. Acad. Ophth.* 90, 1947.
52. Kay, E. B., and Hacker, V. D.: The Treatment of Shock by Aortic Transfusion During Thoracic Operations, *J. A. M. A.* 134:604, 1947.
53. Robertson, O. A., and Bock, A. V.: Memorandum on Blood Volume After Haemorrhage, *Med. Res. Comm. Special Report, Series No. 25*, London, 1919, His Majesty's Stationery Office.
54. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Haemorrhage, *Med. Res. Comm. Special Report, Series No. 27*, London, 1919, His Majesty's Stationery Office.
55. Bobb, J. R. R.: Role of Kidney in Resistance to Ischemic Compression Shock, *Federation Proc.* 6:78, 1947.
56. Hechter, O., Bergman, H. C., and Prinzmetal, M.: Role of Renal Pressor System in Burn Shock, *AM. HEART J.* 29:493, 1945.
57. Moon, V. H.: Renal Deficiency Associated With Shock, *J. A. M. A.* 134:425, 1947.
58. Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L.: Blood Flow, Peripheral Resistance and Vascular Tonus, With Observations on Relationship Between Blood flow and Cutaneous Temperature, *Am. J. Physiol.* 141:518, 1944.
- ✓ 59. Page, I. H.: Arterial Transfusion, *Practitioner* 161:479, 1948.
60. Phemister, D. B., Eichelberger, L., and Lacstar, C. H.: Early Effects on Dogs of Section of the Eighth Cervical Segment of the Spinal Cord and Their Bearing on Shock, *Arch. Surg.* 51:32, 1945.
61. Reinhard, J. J., Glasser, O., and Page, I. H.: Hemorrhagic Hypotension in Hepatectomized and Bilaterally Nephrectomized Dogs, *Am. J. Physiol.* 155:106, 1948.

VENTRICULAR FIBRILLATION INDUCED BY COLD

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A BRIEF direct-current pulse of suprathreshold strength applied to the ventricle late in systole or early in diastole (the "vulnerable period") may often initiate ventricular fibrillation. Fibrillation does not, however, begin immediately, but follows a brief tachysystolic episode during which the stimulated region, acting as a pacemaker, sends out impulses at an accelerating tempo. Fibrillation is a consequence of this tachycardia, and follows any similar tachycardia however generated, whether by low-voltage alternating current stimulation, by rapid induction-shock stimulation, or from discharge of an ectopic focus after occlusion of a coronary artery or drug administration.^{1,2,3} The problem of the "vulnerable period" is thus resolved, not into a question of genesis of fibrillation, but into one of the origin of continuing pacemaker activity at the stimulated region. Thus far, however, no reasons have been advanced why stimulation during the "vulnerable period," and only during this period, should induce pacemaker activity.

When the whole body of the dog or cat is cooled, the heart appears to be more than normally susceptible to the development of ventricular fibrillation. When, instead of the whole heart, a portion only is cooled, by means of a thermode applied to it in situ, the ventricles are rendered even more highly sensitive to fibrillation, which can then almost invariably be produced by mechanical or electrical stimulation which normally would have no effect beyond eliciting ventricular extrasystoles.

The experiments reported here, designed to elucidate the mechanism of ventricular fibrillation as elicited in hearts locally cooled, appear to afford a new approach to the nature of the "vulnerable period."

METHOD

The basic techniques employed in these experiments were as follows: (a) A small (1.0 cm. in diameter) area of the heart was cooled locally by inserting between the heart and pericardium a small, flat thermode through which water at an appropriate temperature could be circulated. Although fibrillation could be evoked by cooling any part of the ventricles, in all of the experiments reported here the cooling was restricted to the lateral wall of the left ventricle,

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These studies were supported by a grant from the Life Insurance Medical Research Fund.

near the apex. (b) The stimuli employed were in all cases slightly supraliminal induction shocks, applied to the ventricle as far as possible away from the cooled region, usually, therefore, at the right lateral base. Because of the distance of the cooled region from the region stimulated, and the strength of the shocks, it can safely be assumed that the shocks were without direct electrical influence upon the cooled area. Moreover, similar results could be obtained by mechanical stimulation of the right ventricle. It is therefore likely that the sole influence of the stimulation on the cooled area was exerted by means of impulses propagated thereto through the ventricular myocardium or other conductive tissue. (c) Electrocardiograms were taken with CV leads, with the chest electrode directly external to the thermode placed at the left apex. The use of this lead makes it possible to locate with some accuracy the point of origin of ectopic ventricular beats, particularly those arising directly beneath the exploring chest electrode, which show exclusively a QS wave as the initial complex. Extrasystoles originating in distant areas exhibit a simple R configuration (Fig. 1), while those from intermediate areas possess Q, R, and S waves of varying amplitudes, Q and S being larger, and R smaller in proportion as the point of origin nears the chest electrode. Other chest leads are equally useful for this purpose, but the standard limb leads permit localization only if Leads I and III are recorded simultaneously.



Fig. 1.—C V lead with the chest electrode on the left chest immediately over the left apex. On the left is a single ventricular extrasystole evoked by stimulation at the lateral margin of the right base, showing a simple R as its initial complex. On the right are two responses to stimulation at the left apex, showing the QS configuration characteristic of extrasystoles arising directly beneath the chest electrode.

Employing the above techniques of cooling, stimulating, and recording, two series of experiments were carried out in fifteen dogs anesthetized with Nembutal, curarized, and ventilated by intratracheal oxygen under slight positive pressure. In the first series, a rhythmic series of single induction shocks was applied to the normally beating and uncooled heart at intervals of one to two seconds. Out of phase with the beat of the heart, they fell at random throughout the cardiac cycle, evoking ventricular extrasystoles whenever they coincided with an excitable part of the cycle. When the whole of a normal

cardiac cycle had been thoroughly explored, stimulation was stopped and cooling started. The electrocardiograph was then started and stimulation reinstituted.

To avoid the interference of supraventricular and ectopic beats (see Fig. 6) and thus simplify analysis, a second series of experiments was devised in which all supraventricular beats were inhibited by stimulation of the vagus, potentiated by physostigmine, to permit maximal reduction of stimulus intensity and thus prevent obscuring the record by artifacts. Against a background of cardiac arrest, paired induction shocks were delivered to the right ventricle by a Lucas pendulum.

RESULTS

Single Impulses in the Normal Cycle.—In no case did ventricular fibrillation follow a single induction shock in uncooled hearts, regardless of the phase of the cardiac cycle in which it was delivered, and whether or not it evoked a response. When responses to stimulation did occur they were characterized electrocardiographically by simple upright initial complexes or R waves interrupting the normal rhythm and followed usually by compensatory pauses. In rare instances they were followed by a single additional ectopic beat of identical configuration, representing, therefore, a spontaneous beat arising from the area of stimulation. (Even induction shocks, if excessively strong, can induce ventricular fibrillation following repetitive responses of the stimulated region, but direct current pulses of somewhat longer duration than induction shocks are far more suitable for its production.)

Single responses to stimulation when the heart was cooled also indicated their distant origin by their simple R configuration. When late in the cycle, or when the cooling was insufficient (above 10° C. in the reservoir of cooling fluid), they were the sole ectopic manifestations, and the results were no different from those in controls with the heart at normal temperature. When, however, the temperature of the cooling fluid was below 10° C., and the extrasystole was evoked early in the recovery cycle, the induced extrasystole was followed by one or more spontaneous extrasystoles whose origin from the cooled area was indicated by a simple QS pattern in direct contrast to the R wave of the electrically induced extrasystole (Fig. 2). These spontaneous extrasystoles at times ceased after one or more beats, but in the majority of experiments they terminated after one to six beats in ventricular fibrillation (Figs. 3 and 4). Although the point was not clear because of difficulty in controlling both variables in sufficient experiments, it seemed that the spontaneous beats that failed to eventuate in fibrillation followed stimulation later in the cardiac cycle and at less cold temperatures.

Ventricular fibrillation, after a short run of tachycardia, was produced in the second series of experiments when two paired impulses were sent into the cooled area of a quiescent heart at intervals corresponding to the "vulnerable"

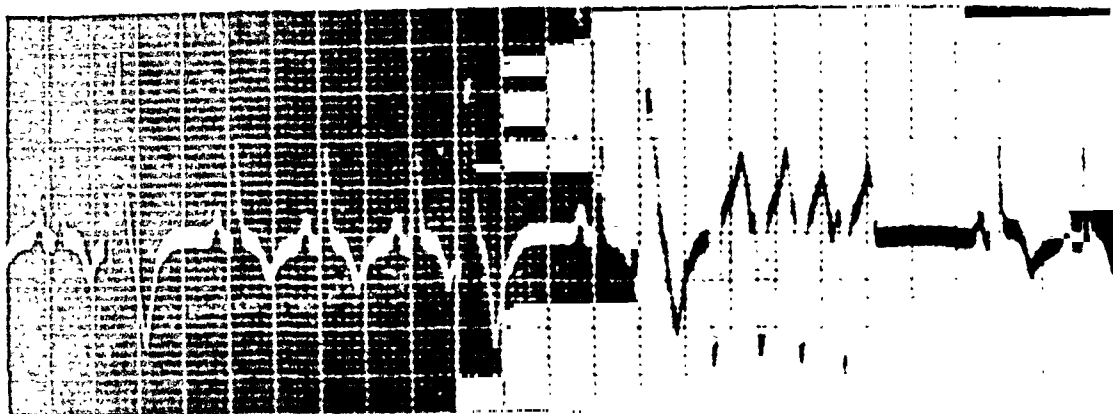


Fig. 2.—C V lead showing a normal cardiac rhythm with a cooled left apex as demonstrated by the inverted T wave. Three ventricular extrasystoles were evoked by stimulation at the right base, and exhibit a characteristic "distal" configuration. The first two are followed only by the expected compensatory pause; the third, which is the earliest of the three in the cycle, is followed by four spontaneous extrasystoles of the very opposite configuration, indicating that they have arisen from the zone of cooling.

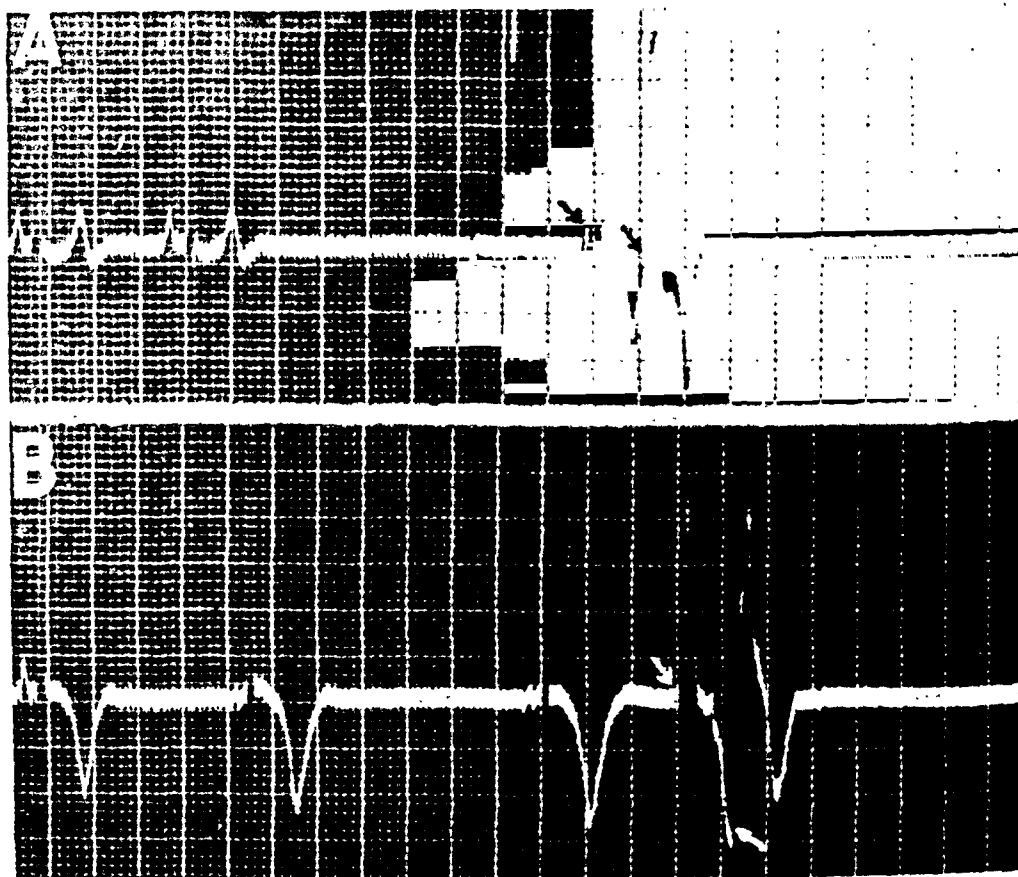


Fig. 3.—A. Control, C V lead, normal temperature as shown by upright T waves. Cardiac arrest by vagal stimulation. Two stimuli at an interval of 0.26 second elicit two responses showing the characteristic R wave of a "distal" extrasystole. B, Early cooling in same experiment. Cardiac arrest by vagal stimulation. The two stimuli still evoke solely the two direct responses originating at the stimulated area.



Fig. 4.—Same experiment as shown in Fig. 3., at successively later stages of cooling. A, The two "distal" extrasystoles are now followed by a single spontaneous response from the cooled area. It arises (see arrow) on the early rising phase of the second T wave. B, Two spontaneous responses marked by arrows follow the two induced responses. C, Four spontaneous responses at an accelerating tempo arise in the cooled area and culminate in ventricular fibrillation.

interval between normal and induced beats in the first series. With lesser degrees of cooling, or slightly longer intervals, it was at times possible to produce a single spontaneous beat or a run of tachycardia which did not terminate in fibrillation.

DISCUSSION

These experiments present in a new light, and suggest an explanation for, the phenomenon of the "vulnerable period" of the cardiac cycle, that period of late systole or early diastole during which a supramaximal electrical stimulus may be followed by spontaneous firing from the stimulated region, culminating in ventricular fibrillation. When a brief direct-current pulse is so applied to the heart as to induce pacemaker activity, at least three effects may be produced at the point of stimulation: (a) anodal or cathodal polarization, (b) reduction of accommodation at the anode and increase at the cathode, and (c) a premature response. In fibrillation facilitated by cooling, these factors are separated. The stimulus to the cooled area is in this case only the normal stimulus of a conducted impulse, and while, from the nature of the cardiac monophasic action potential, the advancing impulse might be considered to act toward the cooled area as a brief direct-current pulse of low voltage, it is more probable that it is in this case the early response rather than the early stimulus that conditions the subsequent repetitive firing from the cooled focus. Expressed in another way, following the sense of the second series of experiments, it can be stated that the reason the stimulation in the vulnerable part of the cycle evokes repetitive firing is that it produces paired responses from an irritable focus at a sufficiently short, and probably critical, interval.

The response to this paired discharge of the cooled area is the development there of a new pacemaker, generating a series of beats which, depending on conditions, either stops or leads to fibrillation. Harris and Rojas³ have stated the reasons for considering that the first few of these beats are in fact separate beats and not already re-entrant beats. To their arguments can be added another, observed in these experiments, namely, that the series may stop after one or more beats without culminating in fibrillation, as De Boer^{4,5} has shown in the frog, and as Harris, Moe, and Wiggers^{1,2} have demonstrated in the mammal. Because of the extreme infrequency of spontaneous arrest in the fibrillating ventricle of the dog, it is unlikely that the early discharges represent re-entrant beats from a circus motion. This confirms the view that the "vulnerable period" concerns pacemaking behavior primarily, and that the fibrillation that supervenes is a response to the accelerating tachycardia.

Other more indirect evidence is afforded by the almost exact reproduction in these experiments, especially in the second series, of observations of Granit and Skoglund⁶ on the effect of cooling the artificial synapse or ephapse. They found that if the sciatic nerve be cut, impulses sent down motor fibers by stimulation of the ventral roots set up "reflected" impulses in the dorsal root fibers by a type of "synaptic" transmission at the cut surface. When this region was cooled, closely paired impulses entering the ephapse evoked not only the

two responses to the "afferent" impulses, but also a spontaneous discharge along the "efferent" fibers arising presumably at the ephapse. In such a preparation there can be no question of circus motion, and the spontaneous discharge can have arisen only from "pacemaker" activity at the ephapse, induced by the arrival there of two closely placed impulses and by the paired responses of the "efferent" limb of the ephapse.

A mechanism that appears able to account for this phenomenon is a combination of two factors: (a) the reduction by cooling of the accommodation of the heart to a constant background stimulus, and (b) the supernormality associated with the negative after-potential. Wedensky first observed the prototype of the latter part of the mechanism in the frog nerve-muscle preparation stimulated subliminally by rapidly repeated shocks applied to the nerve. The muscle could then be thrown into a tetanus by a single impulse conducted physiologically past the subliminally stimulated zone of the nerve. Presumably, the threshold at the subliminally stimulated area was lowered sufficiently during the supernormal period following the single propagated impulse for the latent or subliminal stimulation to become effective. It set up, thus, a second impulse, which was again followed by a supernormal phase permitting a third response, and so on.

In the heart, as in Granit and Skoglund's ephapse,⁶ a single response is apparently not ordinarily followed by intense enough supernormality to set up a new pacemaker, although of course this is precisely what does occur in bigeminy, and in some of the more active preparations of the "artificial synapse" described in an earlier report by Granit and Skoglund.⁷ It is, however, known that "staircasing," that is, increase in the amplitude of the negative after-potential with repetitive firing, can occur to a limited degree in nerve, and is more pronounced, apparently, the shorter the interval between spike responses.^{8,9,10} It is therefore possible that *two* closely paired responses may induce pacemaker activity in a favorable locus through the increment in supernormality evoked by the pairing. In theory, adequate "staircasing" of supernormality, might be expected at times to require more than two, and indeed several, responses, and in fact it has been observed that, especially in preparations that had been fibrillated and defibrillated several times, the sensitivity seemed to become reduced, and as many as three or four impulses were required to induce pacemaker response of the cooled area (Fig. 5).

The fate of such ectopic pacemakers depends on a number of factors. Gasser⁸ has found that while supernormality "staircases" to an early maximum, the subnormality that accompanies the positive after-potential is truly cumulative; and in nerve preparations he has shown how spontaneous repetitive firing based on supernormality can be overwhelmed by the rising tide of subnormality which it engenders. This may well occur in the heart, and account for the cessation of a ventricular tachycardia as well as for the somewhat prolonged pause that succeeds it.

If, however, the "staircasing" of supernormality is progressive for more than a few beats, and if other factors are intense enough to maintain pace-

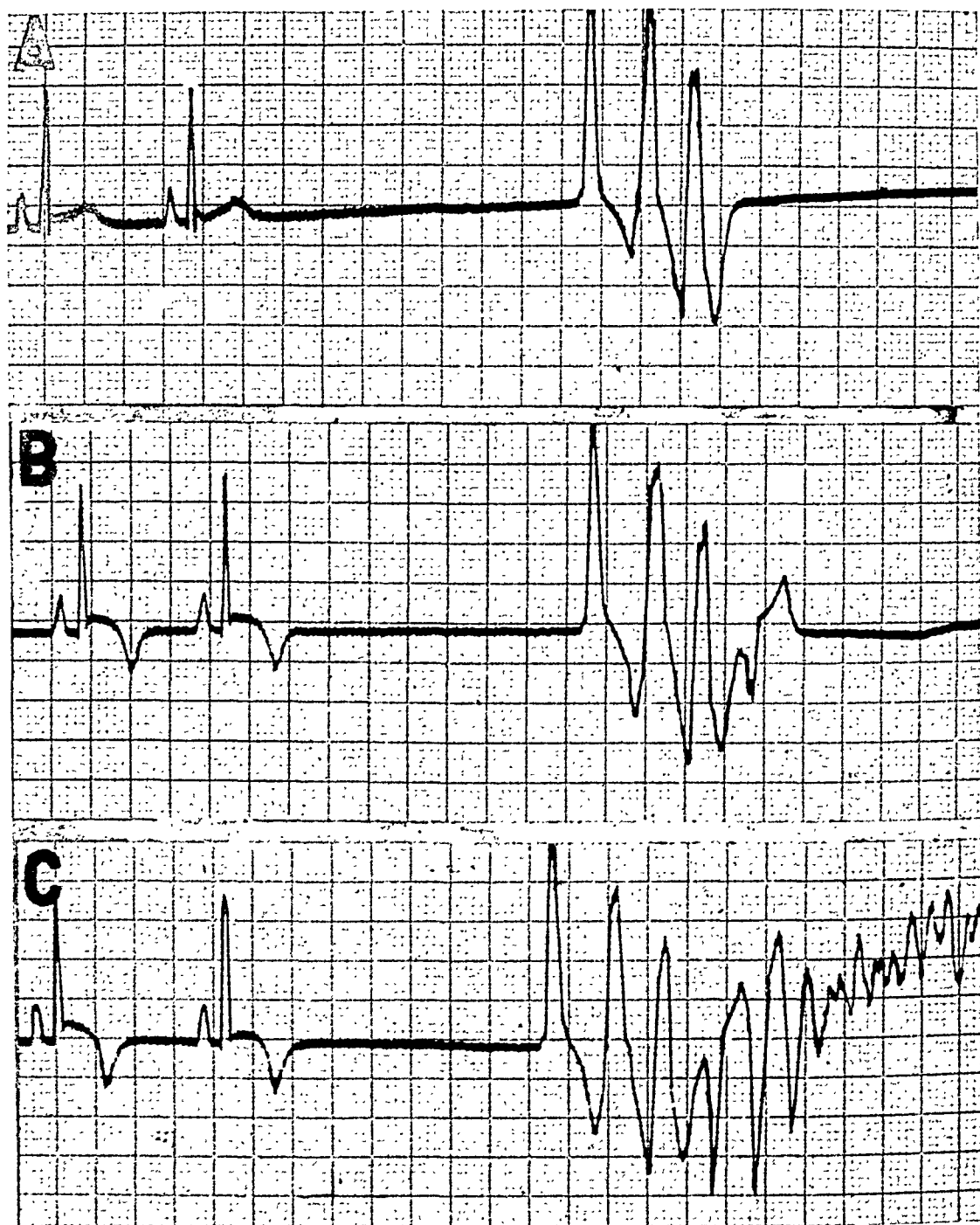


Fig. 5.—A, Three closely spaced responses to stimulation of the right base in a normal heart (upright T waves) arrested by the vagus. B, Early stage of cooling the left apex (inverted T waves). The three responses from stimulation at the right base are followed by a single spontaneous response from the cooled area. C, Later stage of cooling in the same experiment. At least three separate spontaneous responses from the cooled area are seen before fibrillation begins. Here not two, but three closely placed responses are required to induce pacemaker activity in the cooled area.

maker activity, the tachycardia accelerates in rate, because of the shortening of systole with increase in rate and the consequent earlier appearance of supernormality, and fibrillation supervenes. Evidence seems adequate that even in normal hearts an accelerating tachycardia produces regions of physiologic block while other avenues remain open, so that sooner or later an impulse takes a unidirectional course, leaving a route open by which it may return to set up fibrillation. Undoubtedly cooling creates, at the junction between cooled and normal tissue, regions of differing conductivity and differing rates of recovery, which would also facilitate the development of fibrillation. This may account for some instances when fibrillation seems to have begun almost immediately, with little tachysystolic interlude.

The rate of accommodation of many tissues is diminished by cooling, and this presumably also happens in the heart. This would provide an indispensable background for the development of repetitiveness. Accommodation may be defined as the process opposing the excitatory change brought about by a stimulus, and by some it is considered to be identical with cathodal depression.¹² Whatever its nature may be, its effect is to render the tissue unresponsive to a constant stimulus, at a rate characteristic of the tissue and its environmental conditions. The process may be so strongly developed that the tissue will respond but once at the commencement of a constant stimulus; thereafter the stimulus will be ineffective. This is the situation found, for instance, in mammalian motor nerve fibers. On the other hand, tissues that accommodate more slowly or less strongly are able to respond again after recovery from the refractory period left by the first response, and thus a longer or shorter series of repetitive discharges will follow the application of a constant stimulus.

It is known, too, that a cooled region becomes electronegative to normal tissues; this is shown by the large apparent injury currents that develop, reversibly, with local cooling of the mammalian heart,¹¹ and a similar influence of cold has been noted in other tissues.⁶ These two factors provide, then, a constant stimulus, resembling electrotonus, and the reduced accommodation, which combine to permit repeated responses to take place to that constant stimulus, once the threshold has been lowered during the course of the supernormal period following the second of the paired induced responses.

This attempt to explain ectopic phenomena in the mammalian heart in terms of mechanisms observable in simpler excitable tissues such as vertebrate and even invertebrate nerve fibers, and so forth, justifiable as it is even on a priori grounds, and supported by the striking parallel between events at the cooled ephapse and the cooled zone of the mammalian heart, cannot be considered as more than a preliminary exploration of the possibilities, in keeping more with classical neurophysiologic doctrines of rhythmic response than with certain later studies. Invoking as it does the existence of a constant stimulus, eliciting rhythmic discharge because of absence of adequate accommodation to terminate responsiveness of the tissue to the constant stimulus, and spaced by the characteristics of the recovery cycle, it coincides with the account of rhythmic discharge of cut nerve fibers given by Adrian,¹³ where the injury potential at the cut end serves as the constant stimulus, the explanation of dis-

charge in the optic nerve offered by Bernhard, Granit, and Skoglund,¹⁴ according to which the slow retinal potentials provide a relatively constant stimulus, and many others.

The conditioning of rapid rhythmic discharge by supernormality has been commented on by Erlanger and Gasser,¹² and even in crustacean nerves Hodgkin¹⁵ has confirmed the observation that nerves showing pronounced supernormality discharge at rapid and fairly fixed rates when stimulated by constant currents. Axons without significant supernormality discharge repetitively at frequencies that are generally slower and always more variable with change in stimulus intensity.

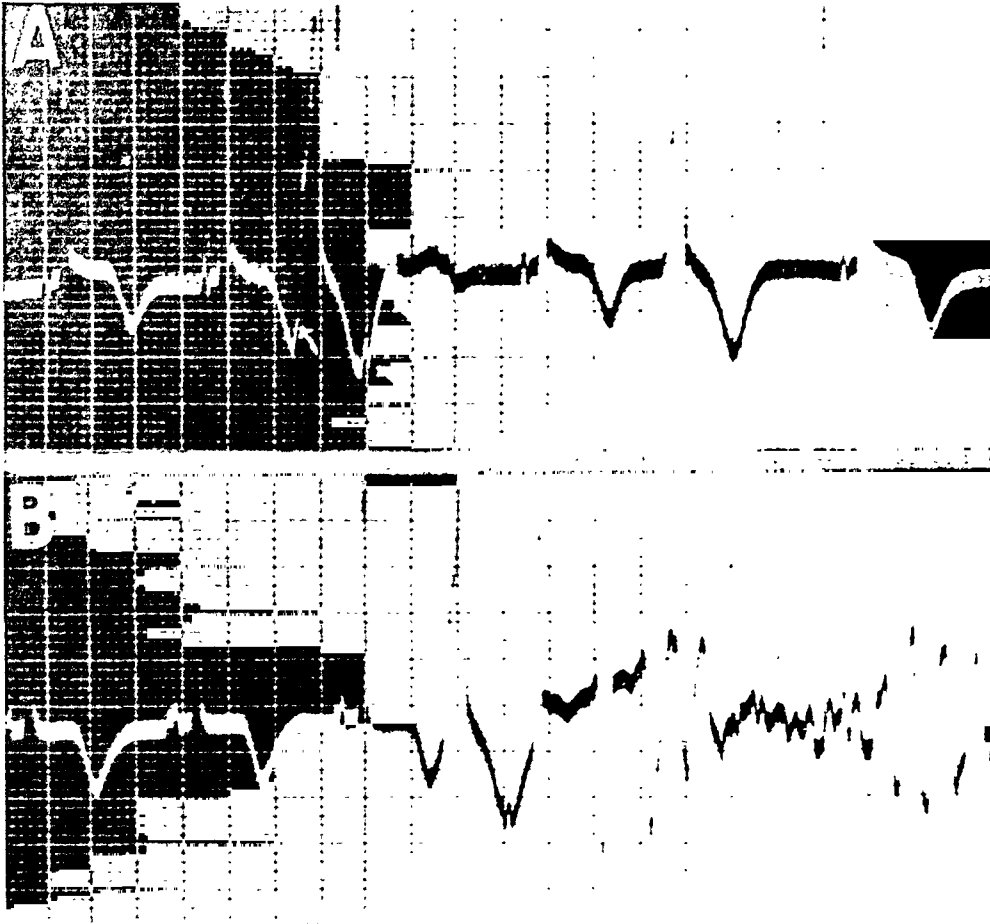


Fig. 6.—A, An interpolated extrasystole in early cooling. The arrows indicate, from left to right, (a) the beginning of the interpolated response, (b) the P wave of the subsequent supraventricular response, and (c) the subsequent normal response after a prolonged P-R interval showing an altered T wave. B, A later stage of cooling. Pacemaker response and subsequent ventricular fibrillation here follow not the induced extrasystole, but a normal supraventricular response, which, because of the interpolated extrasystole, has become the third of a series of closely placed impulses entering the cooled area.

Other factors may, however, be involved in the development and maintenance of repetitiveness at a pacemaker. In a variety of circumstances, as for instance at certain ephapses described by Granit and Skoglund,⁷ a single response may be followed by fluctuations or oscillations of excitability in which

there is in effect rhythmic repetition of supernormal excitability, and this may be great enough to cause spontaneous discharges at the peaks of supernormality. This repetition of supernormal excitability after a response follows the same time course as do spontaneous fluctuations of excitability without previous stimulation, observable in still more unstable tissues, such as nerve in calcium-free solution, and so forth, where again discharges may appear at periods of maximum excitability. The exact relationship of these periodic fluctuations in excitability, and the local electrical potentials with which they are associated, to the classical supernormal period and its accompanying negative after-potential is unclear, but they may well be found to represent one and the same metabolic process. Viewed in this light, the so-called "prepotentials," the presinus waves of Rijlant,¹⁶ the prepotentials of Bozler¹⁷ and others, and the oscillating local potentials of Harris and Moe² partake of the nature of after-potentials. This is in accord with Lorente de No's contention that the negative after-potential and catelectrotonus represent identical processes at the nerve membrane.¹⁸

Hodgkin has recently called attention to a factor he designates as "response-time," which in the crustacean nerve reflects the rate of development of the local potential that triggers the response of the tissue to a constant stimulus. Even in the rapid rhythms conditioned by supernormality this factor appears to be of importance, for the rate does not match the duration of the supernormal period following a single response. While the objection might be raised that the recovery cycle during rhythmic discharge is probably different from that following a single isolated response, and in fact varies with the rate, the work as a whole strengthens the view that factors other than the excitability cycle may contribute to condition the rate of periodic discharge at pacemakers. As Hodgkin points out, a large body of evidence emphasizes the variable nature of repetitive discharges.

SUMMARY

1. Local cooling of the dog's ventricle to 10° c. or below facilitates the development of ventricular fibrillation in response to a single threshold induction-shock stimulation of a noncooled region during early diastole.

2. Fibrillation develops as a terminal event after a short run of ventricular tachycardia, arising in the cooled area.

3. The fact that this series may stop spontaneously before fibrillation occurs indicates that it is in reality a series of separate impulses arising from pacemaker activity in the cooled area, and is not caused by circus motion.

4. Apparently the essential phenomenon of stimulation in the "vulnerable" part of the cycle is that it forces the potential pacemaker to respond at least twice in rapid succession.

5. It is suggested that this reaction presumably sets up spontaneous pacemaker activity in the cooled area by reason of "staircasing" of supernormality, which lowers the threshold sufficiently to produce one or more responses from the cooled area.

6. These responses develop at the cooled area because cooling has produced a potential difference between the cooled and adjacent areas, and they are maintained because the accommodation which normal tissues show to constant currents is reduced by the cooling.

REFERENCES

1. Moe, G. K., Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of Fibrillation by Electrographic Studies, *Am. J. Physiol.* **134**:473, 1941.
2. Harris, A. S., and Moe, G. K.: Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration, *Am. J. Physiol.* **136**:318, 1942.
3. Harris, A. S., and Rojas, A. G.: The Initiation of Ventricular Fibrillation Due to Coronary Occlusion, *Exper. Med. & Surg.* **1**:105, 1943.
4. De Boer, S.: On the Fibrillation of the Heart, *J. Physiol.* **54**:400, 1920-1921.
5. De Boer, S.: On Recurring Extra Systoles and Their Relation to Fibrillation, *J. Physiol.* **54**:410, 1920-1921.
6. Granit, R., and Skoglund, C. R.: The Effect of Temperature on the Artificial Synapse Formed by the Cut End of the Mammalian Nerve, *J. Neurophysiol.* **8**:211, 1945.
7. Granit, R., and Skoglund, C. R.: Facilitation, Inhibition, and Depression at the "Artificial Synapse" Formed by the Cut End of a Mammalian Nerve, *J. Physiol.* **103**:435, 1944-1945.
8. Gasser, H. S.: Changes in Nerve-Potentials Produced by Rapidly Repeated Stimuli and Their Relation to the Responsiveness of Nerve to Stimulation, *Am. J. Physiol.* **111**:35, 1935.
9. Gasser, H. S., and Grundfest, H.: Action and Excitability in Mammalian A Fibers, *Am. J. Physiol.* **117**:113, 1936.
10. Gasser, H. S.: Recruitment of Nerve Fibers, *Am. J. Physiol.* **121**:193, 1938.
11. Personal observation.
12. Erlanger, J., and Gasser, H. S.: *Electrical Signs of Nervous Activity*, Philadelphia, 1937, University Press.
13. Adrian, E. D.: Effects of Injury on Mammalian Nerve Fibers, *Proc. Roy. Soc. London* **106B**:596, 1930.
14. Bernhard, C. G., Granit, R., and Skoglund, C. R.: The Breakdown of Accommodation—Nerve As a Model Sense-Organ, *J. Neurophysiol.* **5**:55, 1942.
15. Hodgkin, A. L.: The Local Electric Changes Associated With Repetitive Action in a Non-medullated Axon, *J. Physiol.* **107**:165, 1948.
16. Rijlant, P.: La conduction dans le coeur du mammifere, *Arch. Internat. de Physiol.* **33**:325, 1930.
17. Bozler, E.: Initiation of Impulses in Cardiac Muscle, *Am. J. Physiol.* **138**:273, 1942.
18. Lorente De No, R.: *A Study of Nerve Physiology*, New York, 1947, Laboratories of the Rockefeller Institute for Medical Research.

PATHOLOGY OF THE INTRAPULMONARY ARTERIES AND ARTERIOLES IN COARCTATION OF THE AORTA ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS

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ABOUT a year ago three of us took part in the study and later in the report of a case of patent ductus arteriosus wherein there were occlusive pulmonary vascular lesions and hypertrophy of the right ventricle.¹ The left ventricle was of normal size. The evidence supported a concept that the right ventricle had functioned as a systemic ventricle; that at times, at least, it had forced blood into the descending aorta. Our interest in the subject of the systemic right ventricle was further enhanced by the subsequent study of yet another case (Case 4 of this paper) in which the right ventricle seemed to have supplied blood to the descending aorta through a patent ductus arteriosus. In this case there had been a coarctation of the aorta proximal to the aortic mouth of a patent ductus arteriosus. There were changes in the intrapulmonary arteries and arterioles which narrowed the lumina of these vessels and so seemed to have caused an increased resistance to pulmonary blood flow.

Because the pulmonary vascular lesions in this case seemed to form an integral part of the circulatory phenomenon wherein the right ventricle assumed a systemic function, it seemed pertinent to make a study of the pulmonary vessels in three other cases of aortic coarctation associated with patent ductus arteriosus, for which material was in our pathologic files. This communication is a report of these three cases as well as of the first case of coarctation and patent ductus arteriosus mentioned. Particular reference will be made to the microscopic changes of the intrapulmonary vessels.

MATERIALS AND METHODS

Four cases formed the basis for this pathologic study. In each patient the gross specimens of the heart and great vessels had been saved and were available for restudy. A rib had been saved from each of two of the patients. In one patient one whole lung had been preserved and in another both lungs were available. In all patients, blocks of lung had been saved in fixative. From these and from the available gross specimens of lung, additional paraffin

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Read before the Twenty-first Annual Meeting of The American Heart Association, Chicago, Ill., June 19, 1948.

blocks and sections were prepared. The original sections and the paraffin blocks from which they had been prepared were also present. From these blocks additional sections were cut and specially stained sections were made.

From each paraffin block that had been saved from the time of the original study of the respective case and from each of the paraffin blocks that were prepared additionally during this study, a section was stained with hematoxylin and eosin stain and another with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. Mallory's phosphotungstic acid hematoxylin stain and a modification of Mallory's aniline blue connective tissue stain were employed, additionally, on a few of the sections.

In addition to a qualitative study of the changes in the pulmonary arteries and arterioles, measurements were made on twenty to forty-five pulmonary arterioles from each patient. Like measurements were made on controls which were taken from normal lungs of ten individuals corresponding in respective age groups to those of the four patients which form the basis of this study. One class of arterioles measured from 50 to 99 microns in external diameter; the other, from 100 to 200 microns. The vessels measured were ones that had been cut at right angles to their long axes.

A few arterioles with maximal changes which occluded their lumina were avoided in performing the measurements. The arterioles were measured according to the following method: Two measurements of the external diameter, adventitia included, one at a right angle to the other, were made and from these the average external diameter was calculated.

Two measurements of the diameter of the lumen were made, one at a right angle to the other, and from these the average luminal diameter was determined. From the determinations each of the external diameter and the luminal diameter the ratio of the luminal diameter to external diameter was calculated.

REPORT OF CASES

CASE 1.—Clinical History: A 15-year-old girl was first seen at the Mayo Clinic when she was 11 years old because of progressive scoliosis. She had always had a normal tolerance to exercise.

On the first admission there was a harsh systolic murmur which was heard loudest at the cardiac apex and over the pulmonary area. In an arm, the blood pressure was 130/82. The eye grounds were normal.

For the treatment of the scoliosis, a spinal fusion by means of a bone graft was carried out on Dec. 29, 1941. The convalescence was uneventful.

The patient returned to the clinic during the fall of 1945 because of continued spinal deformity. The graft made on the first admission was solidly united, but there seemed to be progression of the curvature above and below the graft. The auscultatory signs of the heart were the same as on the first admission. In addition, there was marked accentuation of the pulmonary second sound. The blood pressure was 100/80. On Oct. 25, 1945, further bone grafts were placed in the spinal column.

Postoperatively there was slight dyspnea and slight persistent cyanosis of the left hand. On the sixth postoperative day, without warning signs, the patient lost consciousness and died after being deeply comatose for approximately ten minutes.

On both visits of the patient to the clinic the roentgenograms of the thorax showed evidence of slight cardiac enlargement. The electrocardiograms revealed right axis deviation. On the first visit there were 14.4 Gm. of hemoglobin per 100 c.c. of blood; the value was 13.3 Gm. on the second visit.

The history had been somewhat difficult to obtain as neither the patient nor her parents spoke English. After the patient's death, a physician who spoke their language fluently obtained from the parents the history that for some years there had been intermittent slight cyanosis of the left hand.

Necropsy Findings.—

Gross Observations: The heart, the great vessels, and the vessels of the lungs were of greatest interest pathologically. The great vessels showed two malformations: a patent ductus arteriosus, measuring 0.6 cm. in length and 0.4 cm. in luminal diameter, and coarctation of the aorta. The aortic mouth of the ductus arteriosus lay 3.0 mm. proximal to the zone of aortic coarctation (Fig. 1, *a* and *b*). The appearance of the aorta at the zone of narrowing was typical of that seen in coarctation in that the superior, anterior, and posterior aspects of the vessel showed an external concavity which corresponded in location to a diaphragm-like membrane lying across the lumen of the aorta. In the lower aspect of this membrane there was an opening which admitted only a fine probe. It measured less than 1.0 mm. in diameter and it constituted all of the aortic lumen at the site of coarctation. The aortic mouths of the intercostal arteries were dilated, bearing evidence that a collateral system of arteries existed to bypass the zone of narrowing of the aortic lumen. The entire aorta was then walled and the caliber of the abdominal aorta was narrow. The usual three arteries arose from the aortic arch.

It was of interest that there was no intimal patch in the left pulmonary artery opposite the mouth of the patent ductus arteriosus, a lesion which is common in the usual case of uncomplicated patent ductus arteriosus. Instead, the aortic intima proximal to the coarctation, in relation to the aortic mouth of the ductus arteriosus, was gray and thickened, as though by the presence of an increased amount of fibrous tissue. The pulmonary trunk and its major branches were unusually thick walled. Whereas the wall of the ascending aorta measured 1.0 mm. in thickness, that of the pulmonary trunk measured 1.8 millimeters.

The heart was somewhat enlarged, weighing 310 grams. The weight of a normal heart of a 15-year-old girl is approximately 250 grams. The condition of the right ventricle constituted the chief cause of the enlargement. It occupied an unusually large proportion of the outer surface of the ventricular part of the heart and its wall was considerably hypertrophied, measuring 1.5 cm. in average thickness. The left ventricular wall was only slightly hypertrophied; it was 1.3 cm. thick (Fig. 1, *a* and *b*). The size of the chambers of the atria and of the left ventricle were within normal limits. The right ventricular chamber was moderately dilated.

The mural endocardium of the left-sided chambers and of the right atrium was diffusely thickened to a slight degree; their surfaces were opaque and gray.

The foramen ovale was probe patent. The ventricular septum was closed. The aortic valve was congenitally bicuspid. No anomalies were present in the other valves or great veins.

The pulmonary orifice measured 5.7 cm. in circumference; the aortic, 4.4 centimeters. The lungs, save for absence of the right middle lobe, were not remarkable in gross appearance. There was no atherosclerosis of the larger pulmonary arteries. The remaining viscera were within normal limits. A marked scoliosis to the right involved the vertebral column from the level of the third thoracic to the fourth lumbar vertebra.

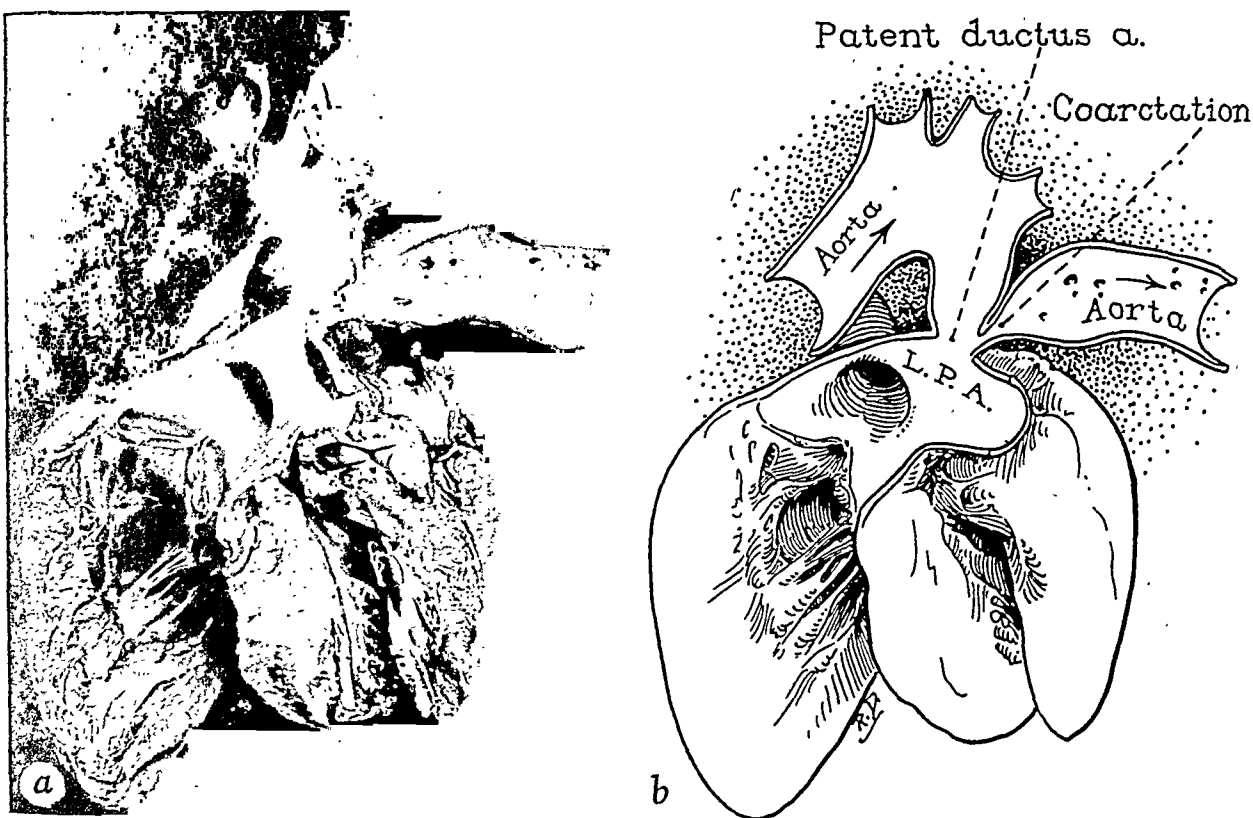


Fig. 1.—Case 1. *a*, The heart and great vessels. Each ventricular wall and chamber is exposed. The pulmonary trunk and the left pulmonary artery have been opened, as has the aorta, except at the zone of the aortic coarctation. The probe lies in the aortic lumen at the level of the coarctation. The right ventricular wall is greatly hypertrophied, exceeding somewhat the thickness of the left ventricular wall, which is slightly hypertrophied. A patent ductus arteriosus joins the lumen of the left pulmonary artery and that of the aorta proximal to the coarctation. In the exposed descending aorta the dilated ostia of the aortic intercostal arteries are shown. The intima of the left pulmonary artery is smooth. A "jet" lesion is lacking in the lower aspect of this vessel, a lesion often seen in uncomplicated cases of patent ductus arteriosus and present in Case 2 (Fig. 2, *a* and *b*). *b*, Diagrammatic sketch of anatomic features illustrated in *a*. L. P. A. means left pulmonary artery.

Since the changes in the intrapulmonary vessels were essentially similar in the first two cases, they will be described after the report of Case 2.

CASE 2.*—*Clinical History*: A 22-year-old man came to the clinic on Dec. 15, 1930, because of a mediastinal tumor. In the five-year period during which the tumor was known to

*This case report is republished with permission from Lemon, W. S.: Case of Congenital Abnormality of the Heart, Coarctation of Aorta and Neurofibroma of Mediastinum, Tr. A. Am. Physicians 46:340, 1931.

be present it had not changed in size, shape, or density, nor had it produced dyspnea. Tolerance to exercise had been normal. Several months before coming to the clinic the patient had begun to have pain in the thorax associated with discomfort when using the left arm. There was nothing in the patient's history to suggest a cardiac or circulatory defect.

Physical examination revealed that the lips were cyanotic to a slight degree. There was a coarse thrill over the sternum at the level of the second intercostal space and the thrill could be felt some distance from this area of maximal intensity. A systolic murmur corresponded to the distribution of the thrill. The cervical vessels pulsated strongly. Pulsations could be felt over the thorax, but the pulsations of the abdominal aorta could not be felt. In an arm the blood pressure was 185/80. The blood pressure in the legs could not be recorded. Electrocardiographic study included only the three standard leads. The results may best be interpreted as indicating left bundle branch block.

The roentgenograms of the thorax revealed a dense circumscribed tumor in the left upper portion of the thoracic cavity. The tumor appeared to displace the left lung downward and the trachea, esophagus, and heart to the right. Several of the ribs showed notching consistent with that seen in coarctation of the aorta, and this diagnosis was made. Surgical exploration for the thoracic tumor was carried out and the tumor which occupied the posterior mediastinum was removed in its entirety. It was found to be a neurofibroma. The patient's immediate postoperative reaction was good, but he gradually failed and died of bronchopneumonia six days postoperatively on Dec. 26, 1930.

Necropsy Findings.—

Gross Observations: The vascular malformations in this case were virtually identical to those in Case 1. There was a patent ductus arteriosus measuring approximately 3.0 mm. in length and 5.0 mm. in diameter, which opened into the aorta just proximal to a point at which aortic coarctation existed. At the zone of coarctation, the aortic lumen measured 2.0 mm. in diameter. In contrast to the finding in the first case, the lower aspect of the origin of the left pulmonary artery and the adjacent pulmonary trunk showed a raised, gray, corrugated intimal patch which measured 1.5 by 1.0 centimeter. It rose somewhat less than 1.0 mm. above the general level of the intimal surface. Microscopically the lesion was characterized by intimal thickening with collagen, fibroblasts, and cells resembling smooth muscle cells (Fig. 2,a and b). It is considered a "jet" lesion representing a reaction to the trauma of a jet of blood directed through the patent ductus arteriosus into the pulmonary arterial system. The usual arterial branches arose from the aortic arch and were wider than normal. As in the first case, the aortic mouths of the intercostal arteries were wide and were considered to represent functioning collateral channels by-passing the aortic coarctation. This was supported by some widening and erosion of the costal groove of the rib which had been removed surgically. This change is seen in cases of coarctation in which there is a well-developed collateral system.

The wall of the ascending aorta was of usual thickness, measuring about 1.8 millimeters. The wall of the pulmonary trunk measured 1.0 mm. in thickness.

The weight of the heart was 626 grams, the expected normal being 275 grams. The enlargement resulted from hypertrophy of each ventricle but particularly the left. The right ventricular wall measured 0.9 cm. in average thickness; the left, 1.8 centimeters. There was moderate dilatation of both

ventricular chambers. The mural endocardium of the left atrium was somewhat thickened, gray, and opaque. The intracardiac septa were intact and there were no anomalies of the great veins. The aortic valve was congenitally bicuspid; its orifice measured 5.0 cm. in circumference. The pulmonary orifice measured 7.0 cm. in circumference. Inferior to the commissure between the right and anterior leaflets of the pulmonary valve there was a small, gray elevation, measuring about 0.3 cm. in diameter, that involved the endocardium of the right ventricle. This resembled an ill-defined endocardial pocket, suggesting morphologically that a degree of pulmonary valvular insufficiency had existed at some period during the life of the patient.

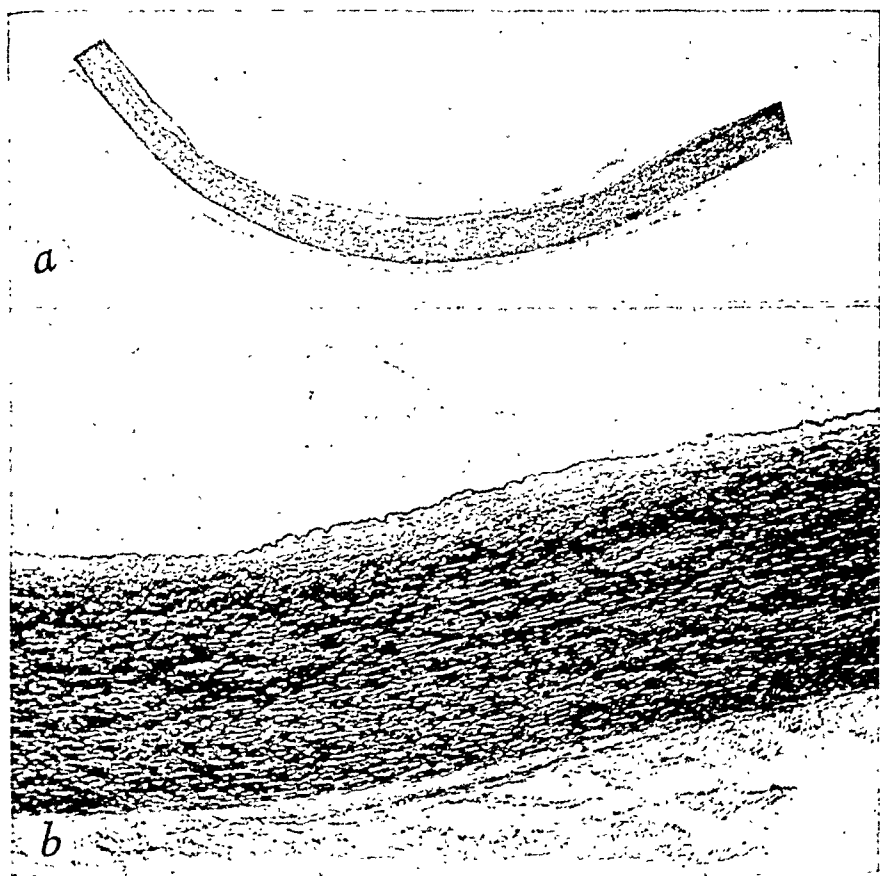


Fig. 2.—Case 2. Sections stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, "Jet" lesion in the left pulmonary artery. Normal intima is shown at the edges of the photograph. The intervening intima is thickened by collagen and cells, some of the latter being fibroblasts; others appear as smooth muscle cells. The lesion is considered a reaction to the trauma caused by a jet of blood entering the left pulmonary artery and traumatizing the intima ($\times 4\frac{1}{2}$). *b*, A portion of the "jet" lesion portrayed in *a* ($\times 25$).

Grossly the lungs were not particularly remarkable. The abdominal viscera showed minor congenital anomalies in the form of unilateral partial duplication of the ureter and a diverticulum of the duodenum.

Microscopic Observations in Cases 1 and 2.—The microscopic changes in the pulmonary vessels in Cases 1 and 2 were essentially alike and will be described

together. The small intrapulmonary arteries showed medial muscular hypertrophy and, frequently, unusually heavy internal elastic laminae were present (Figs. 3,*a* and *b* and 4,*a* to *d*). In some arteries this elastic layer was fragmented and reduplicated, fibers of elastic tissue being intermingled with the smooth muscle of the media (Fig. 4,*c* and *d*). Intimal fibrous thickening in which the fibroblasts and collagen were arranged in concentric layers was a frequent finding (Figs. 4,*a* to *d* and 5,*a* to *c*). In many instances the intimal tissues caused only a slight degree of luminal narrowing. In other vessels they were responsible for considerable narrowing to complete closure of the lumen (Fig. 6,*a*). In Case 2 hyalinization of the media alone was occasionally observed (Fig. 5,*b*), while other arteries in this case showed hyalinization involving the thickened intima as well as the media (Figs. 5,*c* and 6,*a*). Hyalinization of arterial walls was not observed in Case 1. In both cases, in addition to the lesions described, some arteries contained thrombi of varying ages. These were numerous in the first case. In some arteries the thrombi were fresh and organization had just begun (Fig. 6,*b*). In others the lumen was represented by a plexiform arrangement of capillaries lying in dense fibrous tissue, a picture consistent with recanalized thrombi (Fig. 6,*c*). In such instances the effective channel through the vessel was obviously narrowed. In rare arteries in Case 1, at the junction of the media and intima, there were endothelial-lined vessels

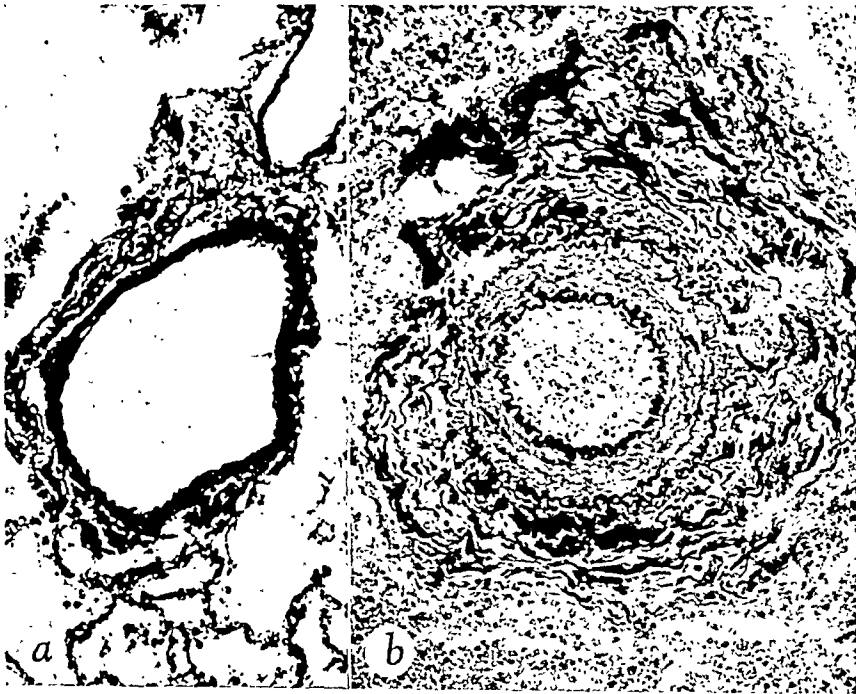


Fig. 3.—Sections stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Control for comparison with Fig. 3,*b*. Normal intrapulmonary artery from a normal lung of a 17-year-old girl ($\times 145$). *b*, Case 2. Intrapulmonary artery showing medial muscular hypertrophy and fibrous thickening of the adventitia. The internal elastic lamina is thick. There is no intimal thickening in this artery. The lumen is relatively narrow for the size of the vessel. Compare with control, Fig. 3,*a* ($\times 145$).



Fig. 4.—Sections of intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Case 1. Prominence of internal elastic lamina. Fibrous thickening of intima. Adventitial fibrosis. The lumen is narrow for the size of the vessel ($\times 185$). *b*, Case 2. Prominence of the internal elastic lamina. Intimal fibrous thickening ($\times 185$). *c*, Case 1. Fragmentation of internal elastic lamina. Shreds of elastic tissue are intermingled with the elements of the hypertrophied media. Intimal fibrosis. Narrowing of the lumen ($\times 225$). *d*, Case 1. Prominence and focal reduplication of the internal elastic lamina. Marked intimal thickening by fibrous tissue causing an extreme degree of luminal narrowing. Adventitial fibrosis ($\times 130$).

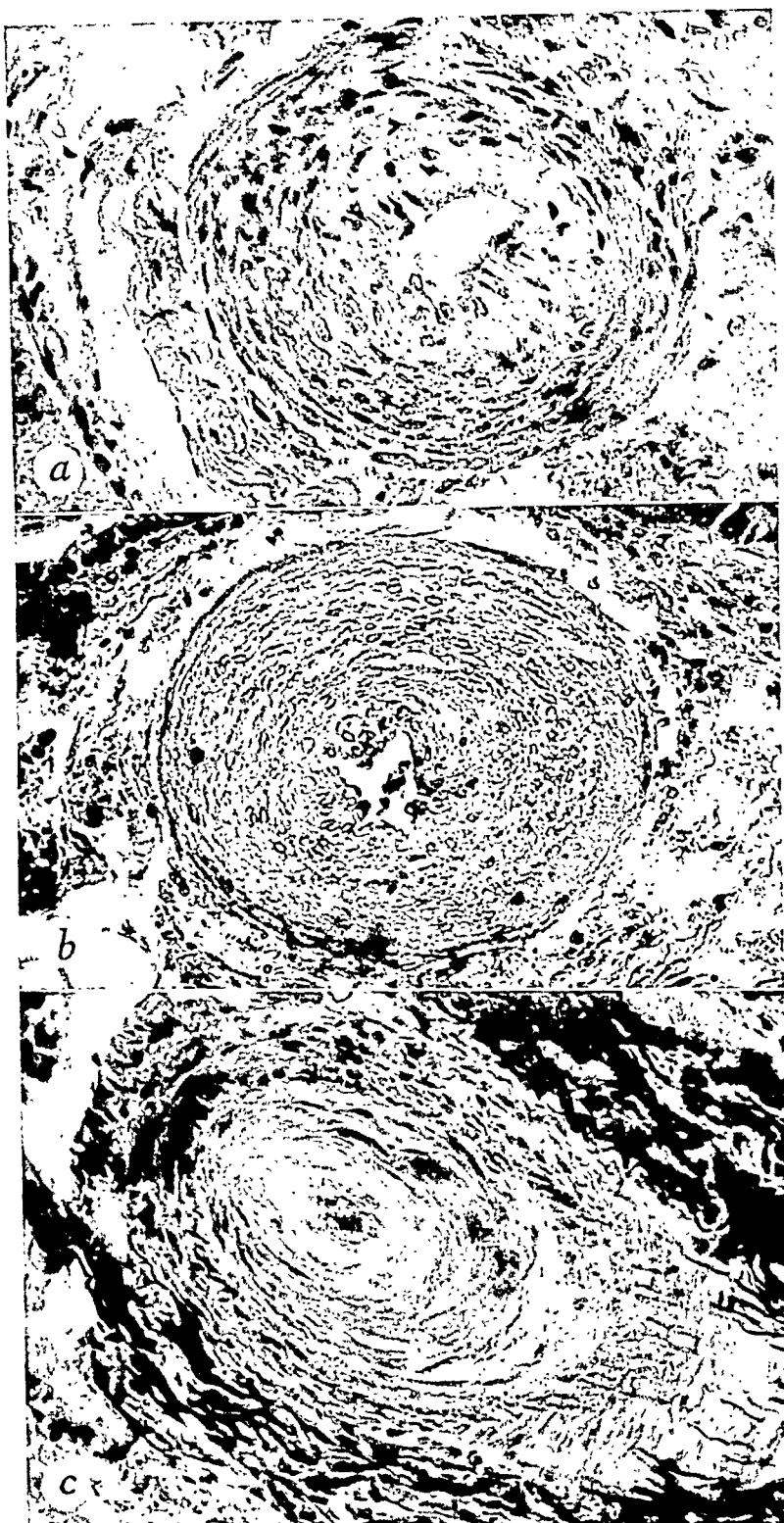


Fig. 5.—Small intrapulmonary arteries. *a*, Case 2. The media is hypertrophic and the intima shows considerable fibrous thickening. These changes cause considerable narrowing of the lumen and thickening of the wall (hematoxylin and eosin, $\times 315$). *b*, Case 2. Luminal narrowing caused by marked concentric fibrous thickening of the wall, particularly the intima. Focal hyalinization of the media (hematoxylin and eosin, $\times 260$). *c*, Case 2. The lumen is virtually occluded by fibrous thickening of the intima. There is hyalinization of the intimal tissue. The internal elastic lamina is fragmented (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, $\times 330$).



Fig. 6.—Sections of intrapulmonary arteries stained with hematoxylin and eosin. *a*, Case 2. The lumen is occluded by fibrous intimal thickening. There is considerable hyalinization of the intimal and medial layers ($\times 570$). *b*, Case 2. The lumen of the artery shown in cross section is plugged by a fresh thrombus. A portion of an artery cut longitudinally is shown. Its lumen contains a mural thrombus which is undergoing organization. The vessel shown in cross section exhibits medial hypertrophy ($\times 170$). *c*, Case 1. The arterial lumen is replaced by a matrix of connective tissue that contains capillaries. The picture is that of an organized and recanalized thrombus ($\times 200$).

containing blood. The intramural vessels could have represented recanalized thrombi or healed small dissecting aneurysms.

In Cases 1 and 2, while the alterations in structure of the intrapulmonary arteries were disseminated and readily evident, many of the arterioles showed only moderate degrees of mural thickening. Rare arterioles showed hyalinization, either diffuse or focal, of their walls.

A few arterioles showed marked medial hypertrophy (Fig. 7,a and b), and adventitial thickening was present in others. A rare vessel of this caliber showed concentric fibrous thickening of its intima, a process which resulted in a considerable degree of luminal narrowing (Fig. 7,c and d). These changes were not numerous, however. None of the arterial and arteriolar lesions were associated with deposits of lipid-filled macrophages. There were moderate degrees of capillary engorgement, but otherwise the capillaries showed no morphologic change. The veins were not remarkable.

Quantitative measurements, recorded in Table I, of arterioles in Cases 1 and 2 revealed that the ratio of luminal diameter to external diameter was reduced as compared to that based on normal controls from individuals of comparable ages. In control arterioles measuring from 50 to 99 microns in external diameter, the lumen comprised 70 per cent of this diameter, while in Case 1 the lumen constituted but 58 per cent of the total diameter of arterioles with similar external diameters. In Case 2 the lumen constituted 53 per cent of the total diameter of arterioles of similar order. Similarly, arterioles measuring from 100 to 200 microns in external diameter showed a reduction in the expected diameters of their lumina. Whereas in the controls the lumina constituted 75 per cent of the total diameter of the arterioles, in Case 1 the lumen comprised 62 per cent and in Case 2 the lumen comprised 58 per cent of the total diameter

TABLE I. COMPARISON OF DIAMETERS OF ARTERIOLAR LUMINA WITH THOSE OF NORMAL ARTERIOLES

EXTERNAL DIAMETER FROM 50 TO 99 MICRONS				EXTERNAL DIAMETER FROM 100 TO 200 MICRONS			
CASE	RATIO OF LUMEN TO EXTERNAL DIAMETER		WIDTH OF LUMEN (PER CENT OF NORMAL)	CASE	RATIO OF LUMEN TO EXTERNAL DIAMETER		WIDTH OF LUMEN (PER CENT OF NORMAL)
	CONTROL	CASE			CONTROL	CASE	
1	.70	.58	83	1	.75	.62	83
2	.70	.53	76	2	.75	.58	77
3	.69	.39	57	3	.75	.40	53
4	.69	.44	64	4	.75	.44	59

Average width of lumina of arterioles of all diameters measured, as compared with average of controls of similar diameters from comparable age groups:
Cases 1 and 2: 80 per cent of control diameter
Cases 3 and 4: 58 per cent of control diameter

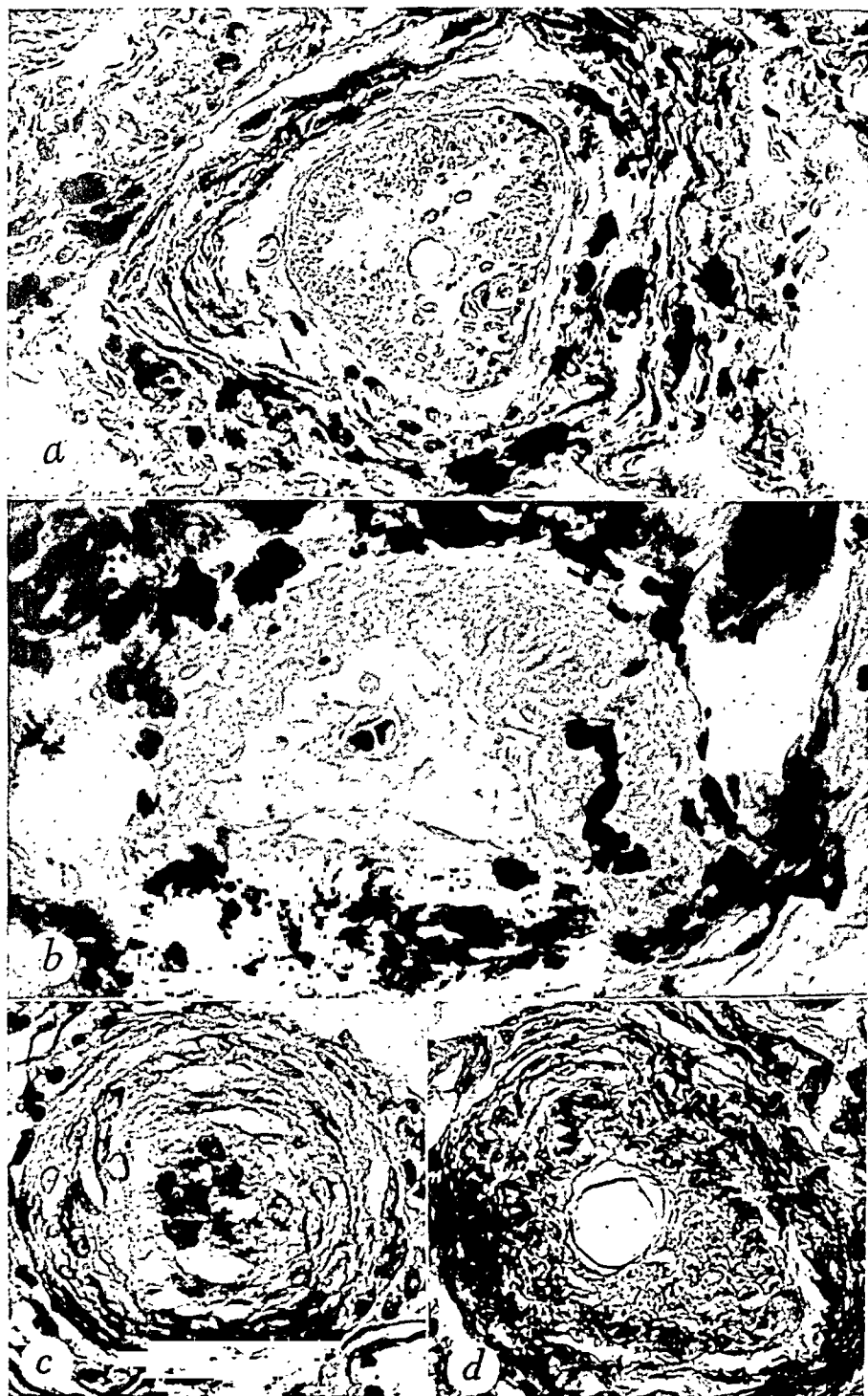


Fig. 7.—Pulmonary arterioles. *a*, Case 1. Medial hypertrophy causing considerable narrowing of the lumen. Adventitial fibrosis (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, $\times 340$). *b*, Case 2. The media shows considerable hypertrophy. The lumen is replaced by a recanalized thrombus (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, $\times 515$). *c*, Case 1. The lumen is greatly narrowed by concentric fibroblastic proliferation of the intima (hematoxylin and eosin, $\times 365$). *d*, Case 1. The lumen is narrowed by intimal proliferation of fibrous tissue. Thickening of the adventitial coat. The internal elastic lamina is prominent in some places and interrupted in others (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, $\times 365$).

of the arterioles. Thus in Case 2 the arterioles with external diameters ranging from 50 to 99 microns showed lumina only 76 per cent as wide as expected and in the same case the lumina of arterioles measuring 100 to 200 microns in external diameter were 77 per cent as wide as the lumina of control arterioles.

Similarly in Case 1 the lumina of the smaller and the larger classes of arterioles were only 83 per cent as wide as the expected normal. If the two classes of arterioles in Cases 1 and 2 are compared with normal arterioles of similar sizes, it is observed that the diameter of the average lumen in these two cases is only 80 per cent as wide as that of normal arterioles.

CASE 3.*—Clinical History: A 23-month-old female infant was admitted to the hospital on June 2, 1923, because of massive generalized edema. Because of respiratory difficulty artificial respiration had been necessary immediately after birth. Her physical development had been retarded. During the five months prior to admission to the hospital she had had fainting spells. No cyanosis had been observed until shortly before admission.

Physical examination showed a poorly nourished child measuring $33\frac{3}{4}$ inches (85.7 cm.) in height. She weighed 23 pounds (10.4 kilograms). There was marked dyspnea and generalized cyanosis. The systolic blood pressure, presumably taken in an arm, was recorded as 90, expressed in millimeters of mercury. The diastolic pressure could not be definitely ascertained.

The heart was enormously enlarged and there was a blowing systolic murmur over the apex. A soft blowing diastolic murmur was heard to the right of the sternum. There were signs of pulmonary congestion as well as massive anasarca and enlargement of the liver.

The infant's condition deteriorated progressively and she died on the sixth day in the hospital.

Necropsy Findings.—

Gross Observations: Examination of the great vessels revealed a coarctation of the aorta associated with a patent ductus arteriosus. In contrast to the lesion in Cases 1 and 2, the coarctation in this case lay proximal to the aortic mouth of the ductus arteriosus (Fig. 8,a). The diameter of the aortic lumen at the zone of coarctation measured 2.0 millimeters. The luminal diameter of the ductus arteriosus measured 2.0 mm. (Fig. 8,b). The aortic mouths of the intercostal arteries were of normal caliber. Since no prominent collateral system of arteries existed, it was interpreted that the aorta below the coarctation had received part of its blood from the aortic arch through the site of aortic narrowing and part through the patent ductus arteriosus from the left pulmonary artery and, ultimately, the right ventricle. As an additional anomaly, the left vertebral artery arose from the aortic arch.

Examination of the heart revealed tremendous enlargement of the right ventricle and a small defect of the membranous portion of the ventricular septum. The heart was enormously increased in weight, weighing 215 grams. The normal cardiac weight for a 23-month-old female infant is 50 grams. The cardiac enlargement resulted mainly from the size of the right ventricle. This chamber constituted the major part of the ventricular portion of the heart, to

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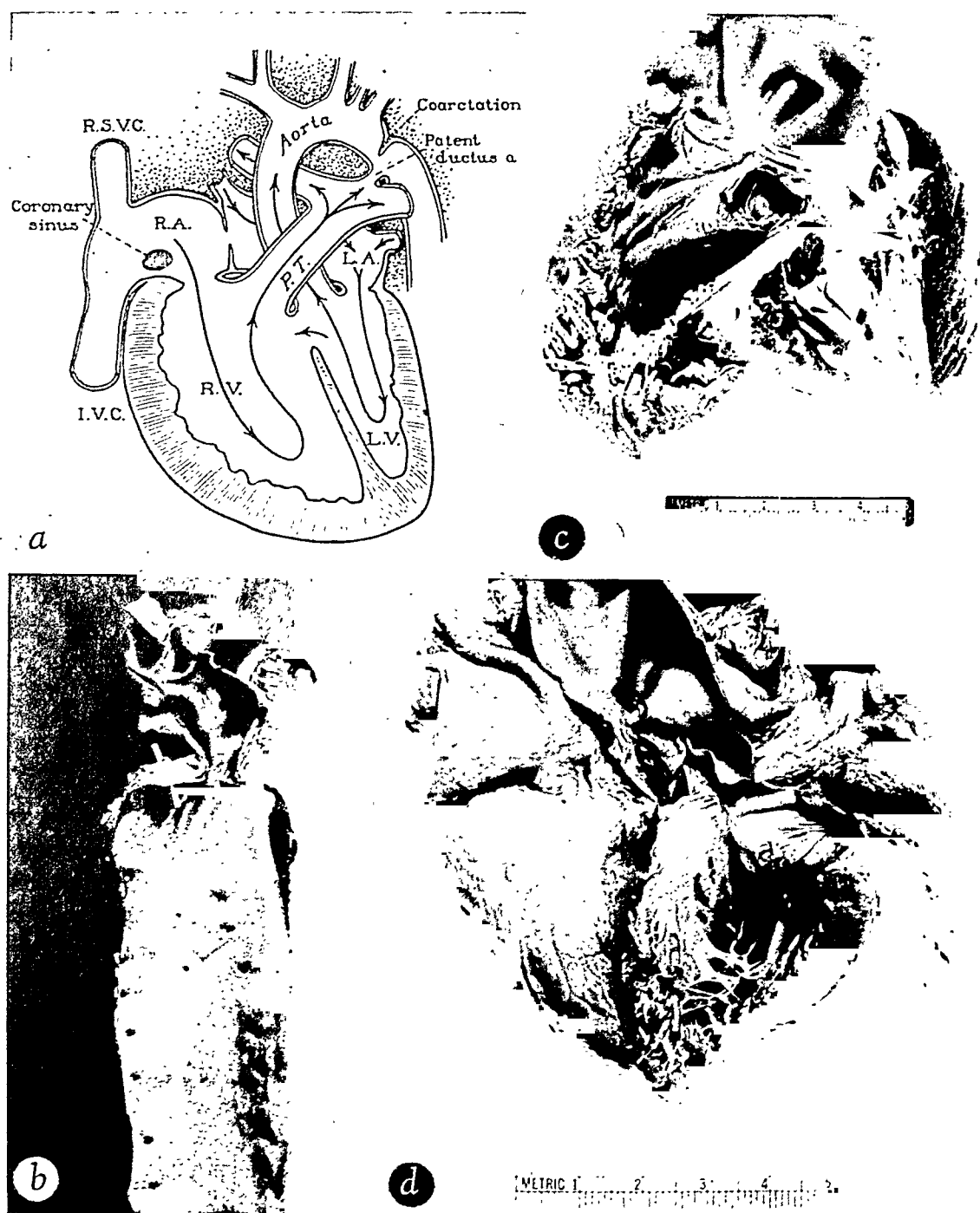


Fig. 8.—Case 3. *a*, The heart and great vessels. There is coarctation of the aorta proximal to the aortic entrance of a patent ductus arteriosus. There is a defect of the membranous portion of the ventricular septum. The right ventricular chamber is enlarged and its wall is hypertrophic. The left vertebral artery arises from the aortic arch. *b*, The thoracic aorta. There is a zone of coarctation proximal to the entrance of a patent ductus arteriosus (probe). *c*, The right ventricle is considerably enlarged. Compare with the left ventricle. *d*, There is an artefact in the subpulmonary region. *d*, The left ventricle. The size of the chamber is within normal limits. The wall is somewhat hypertrophied. The exterior of the right ventricle is seen in the background.

such a degree that the left ventricle, which was essentially of normal size or slightly enlarged, appeared merely as an appendage of the right ventricle. The height of the left ventricular chamber, as measured from the apex of that chamber to the line of attachment of the aortic leaflets, was 4.5 centimeters. From the line of attachment of the pulmonary cusps to the apex of the right ventricle the distance was likewise 4.5 centimeters. The right ventricular chamber was considerably wider than the left. It extended 4.0 cm. to the right of the right surface of the ventricular septum, while the left ventricular cavity extended but 1.3 cm. to the left of the left surface of the ventricular septum. The left ventricular wall measured 0.8 cm. in thickness; the right, from 0.8 to 1.4 cm. (Fig. 8, *c* and *d*). A defect measuring 0.5 by 0.5 cm. involved the membranous portion of the ventricular septum (Fig. 9). Anatomic patency of the foramen ovale was present, the opening measuring 0.7 by 0.2 centimeter. The left atrium was of normal size, while the right atrium was dilated. The pulmonary veins drained into the left atrium. There was a persistent left superior vena cava which entered the coronary sinus at the left border of the heart. The aortic valve was congenitally bicuspid (Fig. 9). The remaining valves were normal. The pulmonary orifice measured 4.8 cm. in circumference; the aortic, 3.0 cm.; the mitral, 4.2 cm.; and the tricuspid, 7.0 centimeters. The lungs were not remarkable in gross appearance.



Fig. 9.—Case 3. Interior of the left ventricle and the aorta. There is a defect in the membranous portion of the ventricular septum. The aortic valve is bicuspid.

In many ways the microscopic appearance of the intrapulmonary arteries and arterioles in this case were identical with those in Case 4. Consequently, the histologic appearance of the pulmonary vessels in these two cases will be described together after the report of Case 4.

CASE 4.*—*Clinical History:* A 7-year-old girl was referred to the clinic on July 1, 1947, by her family physician because of tachycardia. There was no history of rheumatic fever, cyanosis, cough, or thoracic pain. Her exercise tolerance had always been normal.

Physical examination revealed that the patient was normally developed. Blood pressure readings were essentially the same in the two arms, varying from 136 to 150 systolic and from 45 to 50 diastolic. The systolic blood pressure readings in the left leg varied from 98 to 102 and the diastolic, from 50 to 60 mm. of mercury. In the apical region there was a harsh, loud systolic murmur and over the pulmonary area there was a continuous arteriovenous type of murmur. The latter murmur was also heard posteriorly. No thrill was felt on the thoracic wall, but a systolic thrill was palpable over the suprasternal notch. No cyanosis was observed in the lower extremities or in any other part of the body. The femoral arterial pulsations were forceful. Pulsations over the thoracic wall were sought, but none were encountered.

Laboratory studies revealed a trace of albumin in the urine. Examination of centrifuged specimens of urine revealed erythrocyturia, Grade 2 (on the basis of 1 to 4, in which 1 represents the least and 4 the most severe condition). There were 11.3 Gm. of hemoglobin per 100 c.c. of blood. The erythrocyte count was 3,900,000 and the leucocyte count was 6,200 per cubic millimeter of blood. A roentgenogram of the thorax showed cardiac enlargement and prominence of the hilar vessels. There were no erosions of the ribs (Fig. 10,a). The electrocardiogram was unusual and at the time did not contribute to the diagnosis (Fig. 10,b).

The clinical diagnosis was patent ductus arteriosus and coarctation of the aorta. The location of the coarctation with respect to that of the aortic mouth of the ductus arteriosus was not determined.

Operation was advised and it was performed on Oct. 16, 1947. The thoracic cavity was entered through a left posterior exposure. A severe degree of aortic coarctation which virtually closed the aortic lumen was found at a point about 1.5 cm. distal to the origin of the left subclavian artery and just proximal to the aortic entrance of a widely patent ductus arteriosus (Fig. 11,a). Despite the absence of prominent collateral vessels and the fear of irreversible damage from clamping the thoracic aorta for the requisite time to permit an anastomosis, reconstructive surgical treatment was undertaken. The ductus arteriosus was divided and its pulmonary end ligated. The aortic end of the ductus arteriosus was removed along with a segment of aorta containing the coarctation. Anastomosis of the ends of the aorta was accomplished.

The urinary output on the day following the operation was 1,500 cubic centimeters. On subsequent days it varied in amount between 400 and 900 c.c. a day. During the postoperative period the slight albuminuria and microscopic hematuria which had been observed preoperatively were unchanged. On Oct. 20, 1947, thirteen days postoperatively, profound shock developed and the patient died in spite of all measures of resuscitation.

Necropsy Findings.—

Gross Observations: At necropsy it was found that there had been focal separation of the suture line in the aorta which was responsible for a left hemothorax. The heart was greatly enlarged, weighing 250 grams. The normal weight of a heart of a 7-year-old girl is about 80 grams. The cardiac enlargement was caused by hypertrophy of each ventricular wall. The right ventricle measured 0.8 to 1.2 cm. in thickness; the left, from 0.6 to 1.0 cm. (Fig. 11,b). Neither ventricular chamber was dilated. The atria were of normal size and communicated normally with the great veins. The aortic valve was anomalous in that the left and right leaflets were interadherent by a high raphe.

*Certain data in this case report are republished with permission from Burchell, H. B.: Variations in the Clinical and Pathologic Picture of Patent Ductus Arteriosus, M. Clin. North America 32:911, 1948.

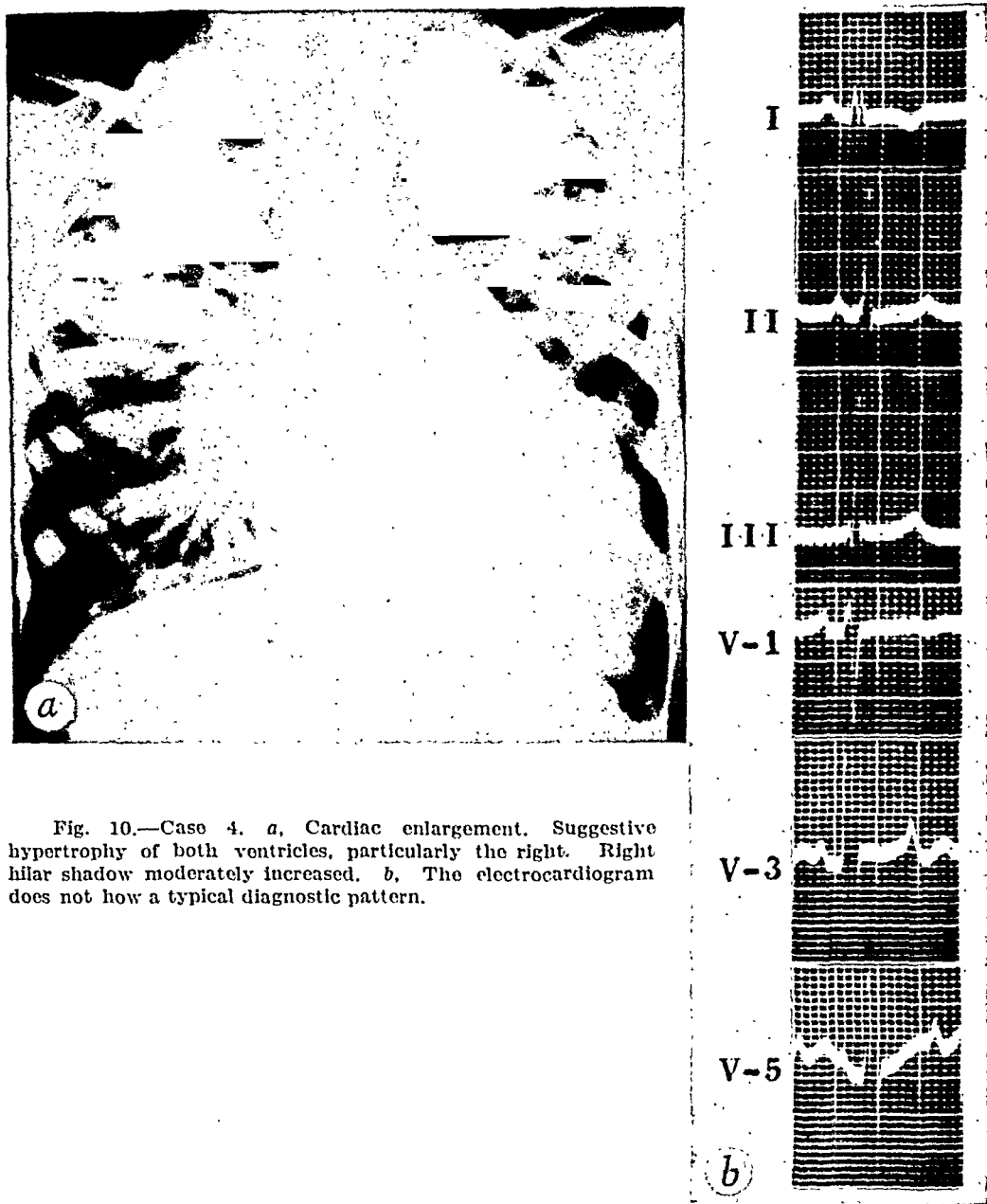


Fig. 10.—Case 4. *a*, Cardiac enlargement. Suggestive hypertrophy of both ventricles, particularly the right. Right hilar shadow moderately increased. *b*, The electrocardiogram does not show a typical diagnostic pattern.

While these two leaflets were identifiable as separate, they must have functioned as a single cusp. The posterior aortic leaflet was normal (Fig. 11,c). There were no other intracardiac anomalies. The pulmonary orifice measured 5.9 cm. in circumference; the aortic, 3.9 centimeters. There was little if any evidence of an enlarged collateral circulation that would bypass the aortic coarctation. The ostium of the first right aortic intercostal artery seemed somewhat wide, but the ostia of the other intercostal arteries were within normal limits of size. The necropsy revealed no evidence of enlargement of the internal mammary or of the epigastric arteries.

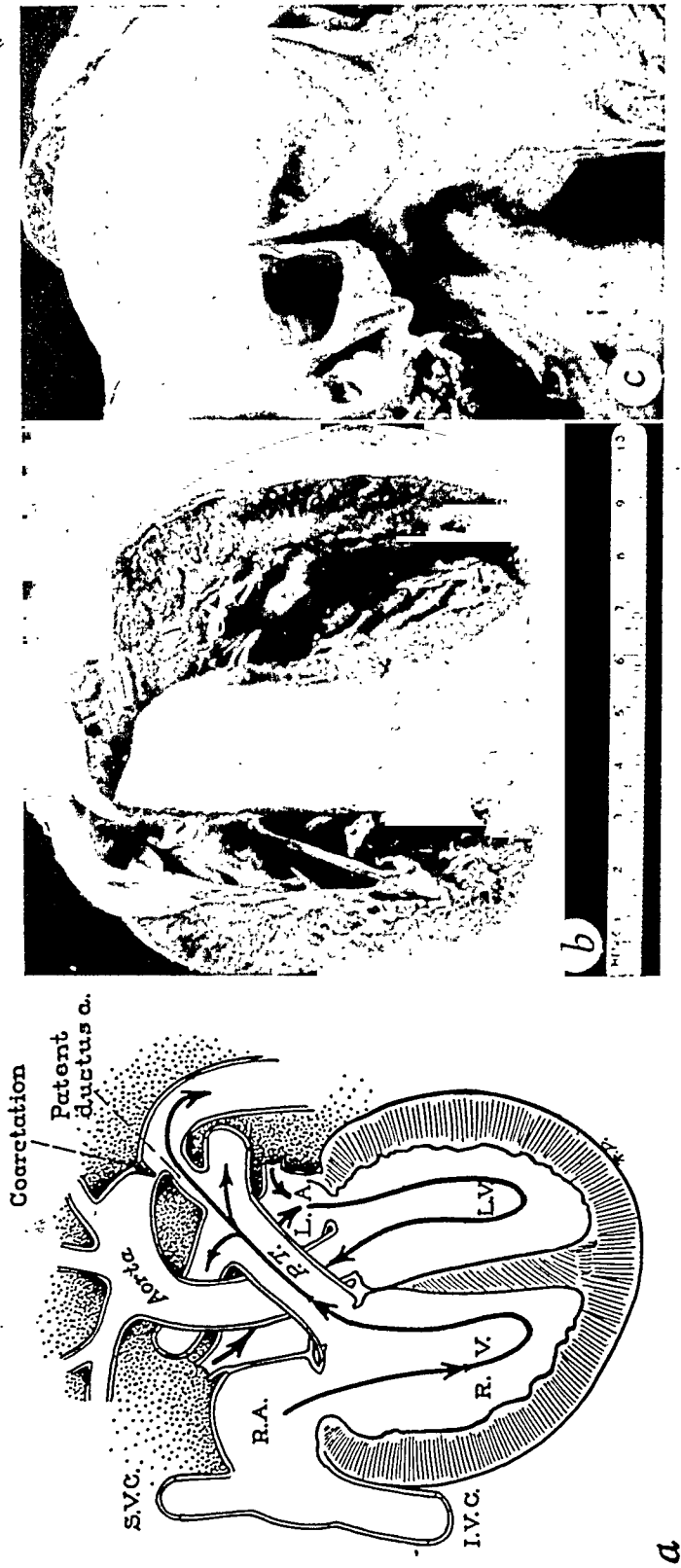


Fig. 11.—Case 4. *a*, The heart and great vessels. Composite of observations made at operation and at necropsy. There is a severe degree of aortic coarctation proximal to the entrance of a widely patent ductus arteriosus. Hypertrophy of right ventricle. *b*, The heart. Each ventricle has been opened. The right ventricle, which functioned as a systemic ventricle, is essentially of the same thickness as the hypertrophied left ventricle. *c*, The aortic valve. The right and left cusps are joined and the two function as a single leaflet rather than as two independent ones. The posterior (noncoronary cusp) is essentially normal.

There were no changes in the ribs such as those seen in the usual type of aortic coarctation. No intimal "jet" lesion was found in the left pulmonary artery. Other than atelectasis of the left lung resulting from the left hydrothorax, the lungs showed no remarkable changes grossly. The kidneys were normal grossly and microscopically.

Microscopic Observations in Cases 3 and 4.—In both Cases 3 and 4 there were morphologic changes involving most of the intrapulmonary arteries and arterioles. The microscopic findings in the lungs in these two cases, which were fundamentally alike, will be described together. Universally, the intrapulmonary arteries and arterioles showed medial hypertrophy. In many instances there were heavy bundles of collagen that constituted the adventitia of these vessels. Intimal changes, to be described, were present additionally in some of the vessels. The media of the intrapulmonary arteries of all sizes showed an abundance of muscle fibers, a phenomenon resulting in thickening of this layer. In addition, in many of such arteries measuring from 500 to 700 microns in diameter there were numerous fibers of elastic tissue intimately intermingled throughout the layer of muscle fibers (Fig. 12,*a, b, and c*). Elastic tissue changes of similar kind but of a lesser degree were observed in arteries of small caliber. The predominant changes in the smaller arteries were adventitial fibrosis and medial muscular hypertrophy. The internal and external elastic membranes stood out clearly, being much more evident than those of normal intrapulmonary arteries of like size (Fig. 13,*a, b, and c*). The changes of the intrapulmonary arteries outlined gave them the appearance of vessels of the greater or systemic circulation rather than of the lesser or pulmonary circulation. The changes described were associated with degrees of luminal narrowing (Fig. 13,*d*).

The arterioles were uncommonly prominent in appearance, a feature resulting from the thick collagenous adventitia and thick media which characterized them. These changes were consistent in all sections prepared from the lungs in both Cases 3 and 4 (Fig. 14,*a to d*). Some intimal changes were present in both cases, but these were particularly evident in the arterioles in Case 3 and in the small intrapulmonary arteries in Case 4. In the arteries the intimal changes, even in Case 4, were spotty. These were characterized by eccentric intimal thickening with dense collagen that contained relatively few fibroblasts (Fig. 15,*a*). No lipoid-filled cells were observed in these lesions. They had neither the appearance of atheromas nor that of organized thrombi. Arteriolar intimal changes were widespread in Case 3 (Fig. 15,*b and c*). These were characterized by the presence of concentric layers of fibroblasts that formed configurations which resembled the "onion peel" changes seen in peripheral arterioles in cases of malignant hypertension and in the pulmonary arterioles in certain cases of mitral stenosis.² The effect of the intimal fibrosis was to thicken the intima greatly and to narrow the lumen to the point of complete closure. In Case 4 a rare small artery contained an organizing thrombus. No completely organized or recanalized thrombi were found in either of the two cases. In Case 3 engorgement of the alveolar capillaries was present in small foci, but most areas were free of this change. In Case 4 a moderate amount of

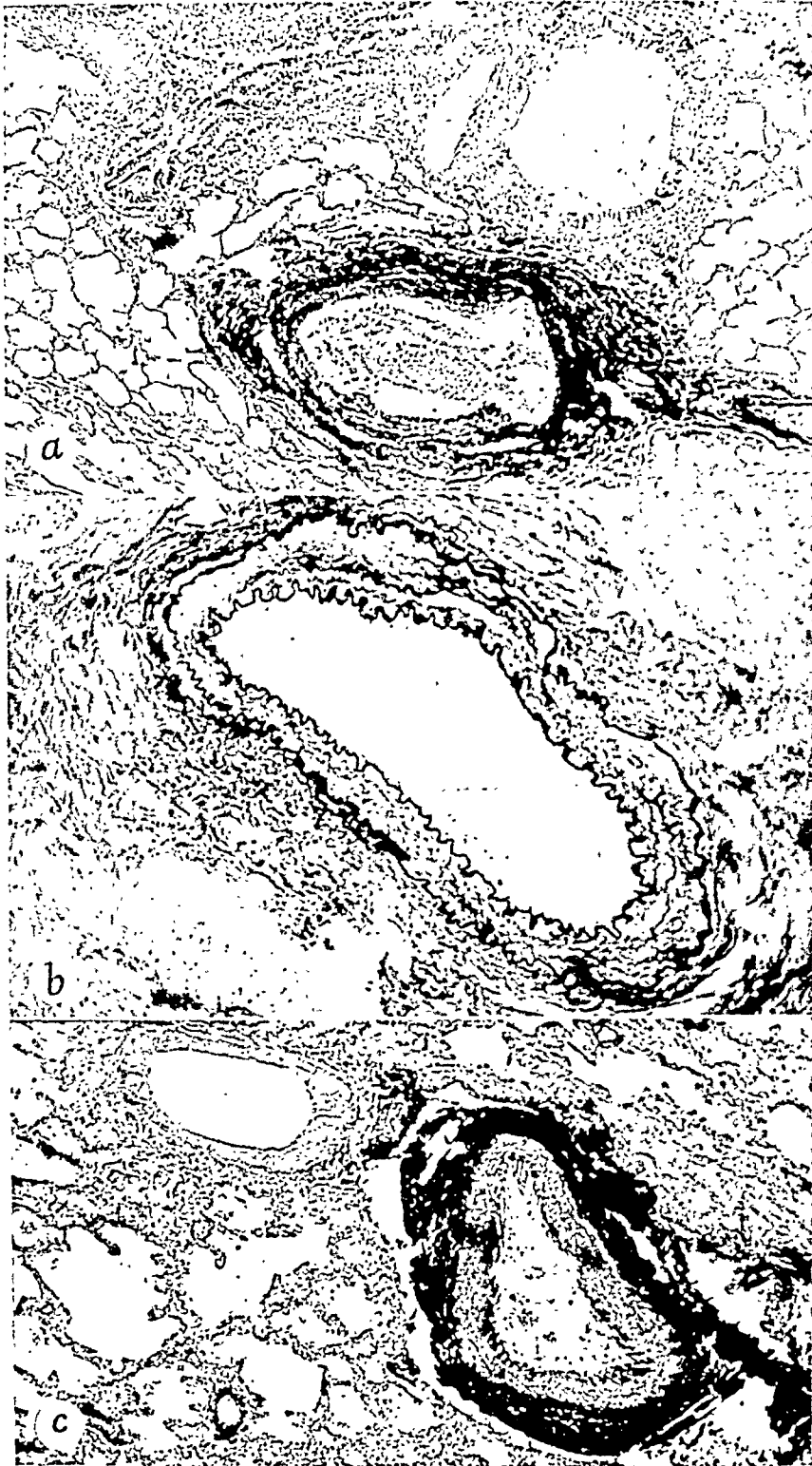


Fig. 12.—Sections of intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counter-stained with Van Gieson's connective tissue stain. *a*, Case 3. The media shows muscular hypertrophy and it also contains numerous elastic tissue laminae. There is some increase in adventitial connective tissue (X30). *b*, Case 4. Essentially the same medial and adventitial changes as shown in Case 3, illustrated in *a*. The medial structure is similar to that of the elastic branches of the aorta rather than to a normal pulmonary artery of like caliber (X75). *c*, Case 3. Medial hypertrophy and adventitial fibrosis (X60).

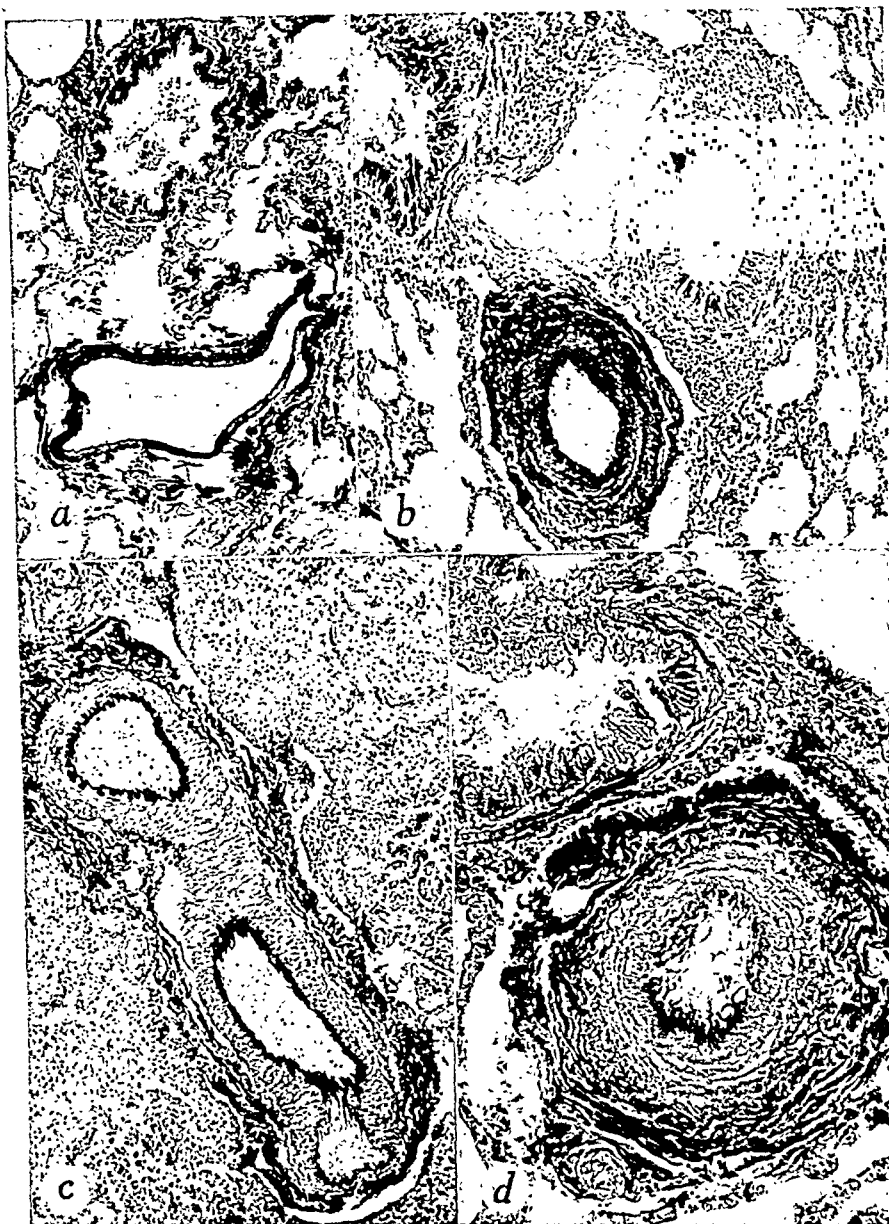


Fig. 13.—Sections of small intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Normal artery from a 2-year-old boy for comparison with artery of similar size from Case 3 shown in *b* ($\times 55$). *b*, Case 3. The lumen is relatively narrow. The media is hypertrophic and the internal and external elastic laminae are prominent. There is adventitial fibrous thickening. The intima is normal in this artery. Compare with *a* ($\times 55$). *c*, Case 4. As in Case 3, the artery shows medial hypertrophy and adventitial fibrosis. The artery appears more like a peripheral artery than a pulmonary artery. The vessel is tortuous ($\times 65$). *d*, Case 3. Medial hypertrophy and adventitial fibrosis associated with luminal narrowing ($\times 200$).

congestion was evident. This may have been related to the state of shock that existed prior to death. In neither Case 3 nor Case 4 was there any fibrous thickening of the alveolar walls, or any interstitial edema. There were no histologic changes in the tributaries of the pulmonary veins.

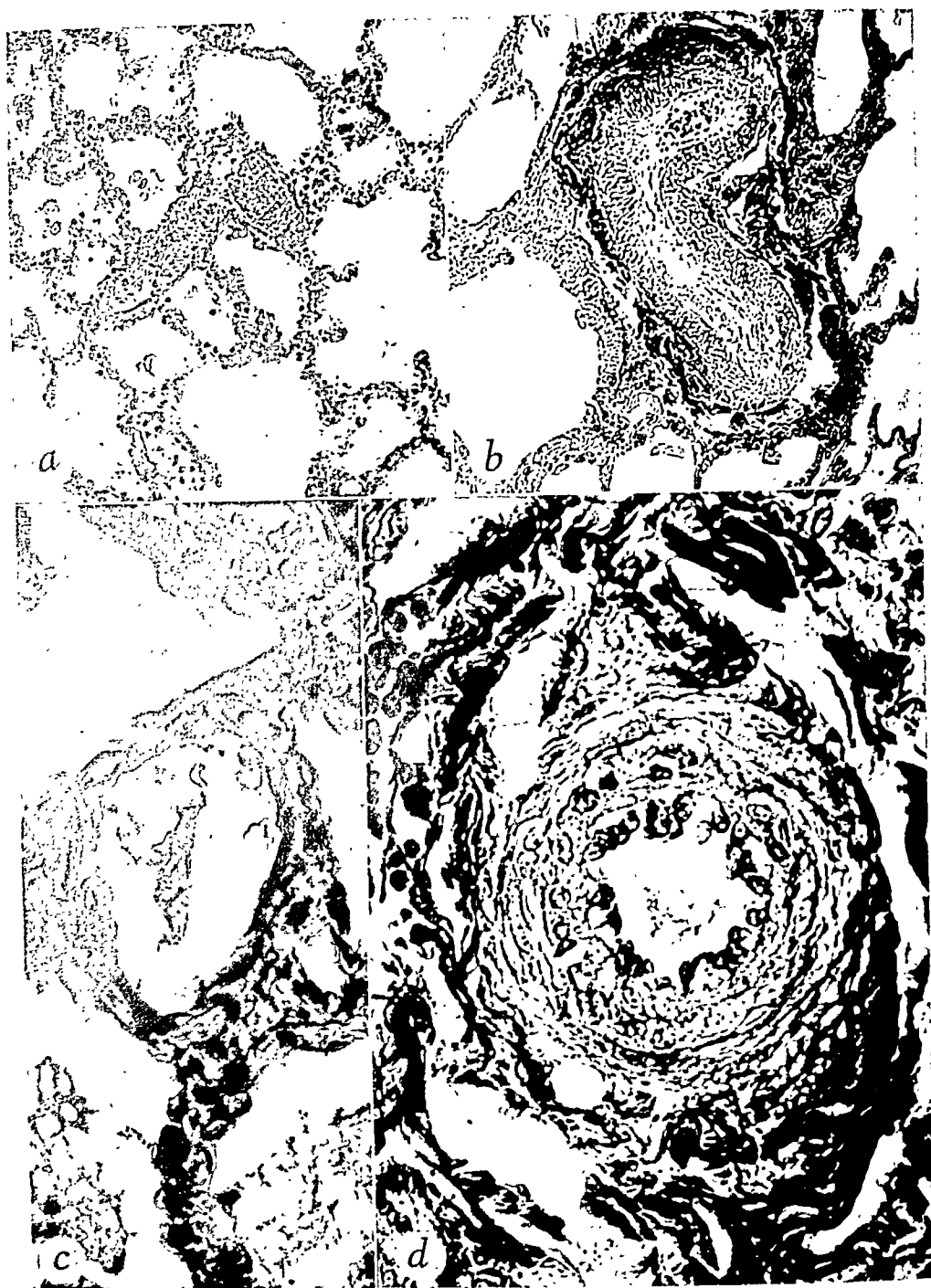


Fig. 14.—Sections of pulmonary arterioles stained with Verhoeff's elastic tissue stain and counter-stained with Van Gieson's connective tissue stain. *a*, Normal pulmonary arteriole from an 18-month-old infant for comparison with one in Case 3, illustrated in *b* ($\times 115$). *b*, Case 3. Thickening of the arteriolar wall chiefly as a result of medial hypertrophy. There is also some intimal and adventitial fibrosis. Considerable luminal narrowing. Compare with normal illustrated in *a* ($\times 115$). *c*, Normal pulmonary arteriole from a 6-year-old child for comparison with one in Case 4, illustrated in *d* ($\times 435$). *d*, Case 4. Medial hypertrophy of arteriole. Adventitial fibrosis. Swollen endothelial cells. Luminal narrowing. Compare with *c* ($\times 435$).

As in Cases 1 and 2, measurements of the arteriolar luminal diameters were compared with those of normal pulmonary arterioles from individuals of ages corresponding to those of the particular subjects. The degrees of arteriolar luminal narrowing were more severe in Cases 3 and 4 than they were in Cases 1 and 2. The results are recorded in Table I. In Case 3, in which the greatest degree of arteriolar luminal narrowing occurred, the diameters of the lumina of arterioles for which the external diameters ranged from 50 to 99 microns



Fig. 15.—*a*, Case 4. An intrapulmonary artery showing medial hypertrophy, focal interruption of the internal elastic lamina, and focal intimal thickening with fibrous tissue (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, $\times 170$). *b*, Case 3. Pulmonary arteriole showing marked luminal narrowing on the basis of laminated cellular fibrous thickening of the intima and medial hypertrophy (hematoxylin and eosin, $\times 460$). *c*, Case 3. Pulmonary arteriole. The lumen is greatly narrowed by the cellular changes in the thickened wall. There is intimal fibrous thickening and medial hypertrophy (hematoxylin and eosin, $\times 620$).

averaged 57 per cent of the control diameters. In that case the arterioles which measured 100 to 200 microns in external diameters showed lumina, the diameters of which averaged only 53 per cent of the control diameters. While in Case 4 the arteriolar lumina were not narrowed to the degree that existed in Case 3, they were, nevertheless, significantly narrowed. Thus, in arterioles with external diameters varying from 50 to 99 microns the arteriolar lumina were only 64 per cent as wide as the expected. In the class of larger arterioles in Case 4 the lumina were 59 per cent as wide as in control arterioles of comparable external diameters. If one averages all the arterioles measured in Cases 3 and 4, he derives the fact that the average arteriolar lumen in these two cases was only 58 per cent as wide as the average control arteriolar lumen.

COMMENT

It is of interest to discuss the aberrations of circulation in our four cases. In none had special intracardiac and intravascular studies been carried out during the respective lives of the patients. Such studies might have established certain facts from which positive deductions concerning pulmonary arterial pressures and directional flow could have been made. Nevertheless, there are sufficient morphologic alterations to justify such a discussion. Cases 1 and 2 will be considered first. It will be recalled that the basic malformation in each was the presence of aortic coarctation at a point distal to the entrance of a patent ductus arteriosus. What might have been the circulatory status of these two individuals during fetal life? Under conditions of normal fetal circulation the pressures within the two ventricles are probably equal as they are in the pulmonary trunk and its major branches on one hand and in the aorta on the other. The ready communication of the pulmonary arterial system with the aorta through the ductus arteriosus is one important factor in equalizing the pressures. Another factor is that of the intrapulmonary vessels which either by their structure or their function or both act as a sphere of relatively high resistance and so tend to divert blood through the ductus arteriosus into the descending aorta. Relatively little blood flows through the fetal pulmonary circulatory system compared with that which flows through the ductus into the aorta. We assume that the coarctation existed before birth. Thus during fetal life the right and left ventricles were in direct communication with the aorta above the coarctation. Two modes of fetal circulation may be considered. The first would have been dependent upon a greater pressure in the aortic arch than in the pulmonary arterial system. Under such circumstances the blood flowing through the ductus arteriosus would have been directed toward the left pulmonary artery, a direction the reverse of the normal for the fetus.³ From the pulmonary arteries the blood would flow through the lungs and return to the left ventricle, whence it would again enter the aorta above the coarctation. An avenue for the free flow of blood in the course outlined would probably have resulted in an aortic pressure insufficient to stimulate the formation of adequate collaterals. In that event the aorta below the coarctation would have received little blood and the flow through the placenta would have been inadequate.

quate to maintain life. Since both of these individuals did have a complete fetal life, it is evident that during that period there had existed an adequate placental flow. That being the case, the conjectural course of the circulation as it has been outlined must not have been in existence.

The second alternative would have been for collateral channels to have developed to sufficient size to carry an adequate amount of blood into the lower part of the aorta. Such a collateral system existed at the time of necropsy at the ages of 15 and 22 years, respectively. That it had actually functioned while the individuals were in utero is attested to by the fact that life during that period was normally maintained. The development of a collateral system such as exists in coarctation is probably dependent upon the maintenance of a substantial blood pressure above the point of aortic narrowing. One must therefore assume that in our Cases 1 and 2 a substantial blood pressure existed in the upper part of the aorta before birth. Since the pulmonary circulation was in communication by way of the ductus arteriosus with the aorta proximal to the coarctation, there must have been sufficient resistance to pulmonary blood flow so as to support, in the proximal part of the aorta, a pressure sufficient to stimulate the formation of adequate collaterals. In a circulatory system functioning as outlined, the flow of blood in the fetal ductus arteriosus would be in a normal direction, from the left pulmonary artery into the aorta.

It is evident that the discussion of the fetal circulation in our Cases 1 and 2 pertains, as well, to all cases of coarctation of the aorta wherein the coarctation lies at a point distal to the aortic mouth of the ductus arteriosus. Under usual conditions in the individual born with this type of coarctation, the ductus arteriosus closes normally during the early postnatal period and the lungs are no longer the potential site of a shunt of blood coming from the aorta through the ductus arteriosus. In our Cases 1 and 2, on the other hand, the ductus arteriosus remained open. In the face of the normal postnatal differences between the aortic and pulmonary pressures one would expect that aortic blood would be shunted into the lungs through the ductus arteriosus. Adding the factor of hypertension as it exists in coarctation, the degree of the shunt in our Cases 1 and 2 would, all other conditions being equal, be of considerable magnitude. That such was the case for some time after birth cannot be denied, but for some time before death there were lesions in the pulmonary arterial tree which were obstructive in nature. On the basis of these lesions it is expected that the degree of resistance to pulmonary flow must have been greater than normal. Such a factor would tend to reduce the effective difference in pressures between that in the aorta on one hand and that in the pulmonary arterial tree on the other. In Case 2, in spite of the pulmonary vascular lesions mentioned, the flow through the ductus arteriosus seems to have been from the aorta into the left pulmonary artery. The evidence for this assumption lies in the fact that the associated cardiovascular lesions were essentially like those seen in cases of uncomplicated patent ductus arteriosus. These were the marked degree of left ventricular hypertrophy coupled with only a slight degree of enlargement of the right ventricle and the presence of a "jet" lesion in the left

pulmonary artery. The assumption is further supported by the high pulse pressure that had existed in the peripheral arteries during life.

The situation in Case 1 with respect to the direction of flow through the ductus appears different from that in Case 2. In Case 1 there was considerable right ventricular hypertrophy, the right ventricular wall exceeding the left with respect to thickness, and there was some dilatation of this chamber as well. The absence of a "jet" lesion in the left pulmonary artery may be used as evidence favoring the concept that if the direction of flow in the ductus arteriosus was from the aortic to the pulmonary side, the volume of such flow was not great. The presence of intermittent cyanosis of the left hand suggests that from time to time, at least, pulmonary arterial blood was entering the aorta and part of that blood found its way into the left subclavian artery, the aortic mouth of which lay opposite that of the ductus arteriosus. The low pulse pressure in the peripheral circulation is evidence favoring the hypothesis that there was probably little if any escape of aortic blood through the ductus arteriosus. The other evidence cited favors the idea that if any shunt did occur through the ductus arteriosus in Case 1 it was in the direction of pulmonary artery toward the aorta. Such a vascular phenomenon would, of course, require that the resistance to pulmonary flow be equal to or greater than the peripheral resistance. The vascular lesions in the pulmonary arterioles and the small arteries are believed related to, and indicative of, such an increased resistance. In Case 1 the load to which the right ventricle was subjected appears to have been equal to, or greater than, that of the systemic left ventricle.

The fetal circulation in Cases 3 and 4, wherein the coarctation of the aorta was proximal to the aortic entrance of the ductus arteriosus, differed profoundly from that in Cases 1 and 2, in which, as described, the coarctation was distal to the aortic mouth of the ductus arteriosus. Whereas in Cases 1 and 2 the fetal circulation varied from the normal in that an adequate collateral system had to be developed to maintain life, the fetal circulation in Cases 3 and 4 varied little, if at all, from that of the normal fetus.

In the normal fetus, that portion of the aorta known as the isthmus, which lies between the left subclavian artery and the aortic entrance of the ductus arteriosus, is quite narrow. On this basis it is felt that most of the blood which leaves the fetal left ventricle flows into the arteries arising from the aortic arch. Thus, very little left ventricular blood passes through the aortic isthmus into the descending aorta. On the other hand, a substantial portion of the blood which leaves the right ventricle flows through the ductus arteriosus into the descending aorta. Stated another way, the great proportion of blood in the descending aorta of the normal fetus is derived by way of the ductus arteriosus from the right ventricle.

During fetal life in our Cases 3 and 4, therefore, the presence of aortic coarctation proximal to the ductus arteriosus altered the circulation little, if any, from that in normal fetuses. In the normal fetus, as in Cases 3 and 4 during fetal life, the resistance to blood flow in the pulmonary circuit is either equal to or greater than the peripheral resistance. Normally at birth, as the

placental circulation is removed, the resistance to peripheral blood flow rises. At the same time the establishment of full pulmonary blood flow is associated with decreased resistance to pulmonary blood flow. These two factors seem largely responsible for a great disproportion between the peripheral and pulmonary blood pressures after birth. As a result of these pressure differences, even when the ductus arteriosus remains patent, the right ventricle no longer forces blood into the descending aorta.

On the contrary, in the ordinary case of persistent patency of the ductus arteriosus, the flow after birth is from the aorta into the pulmonary arterial system. In unusual cases of patent ductus wherein there are obstructive lesions in the pulmonary arteries and arterioles, evidence indicates that the resistance to pulmonary flow may be of such proportions that the right ventricle builds up pulmonary arterial pressures which equal or exceed the pressures in the aorta.^{1,4} When this happens, the flow of blood through the ductus arteriosus from the aorta into the left pulmonary artery may be materially reduced or the flow in the ductus arteriosus may be reversed, the right ventricle forcing blood into the aorta. In such a case the right ventricular wall is hypertrophic and may exceed the left ventricle in thickness. In our Cases 3 and 4 the presence of coarctation at the aortic isthmus prevented normal dilatation of this zone of the aorta after birth. In the face of absence of obvious collateral channels, and in the presence of a patent ductus in each of these cases, it is strongly suggestive that the right ventricle continued after birth to supply blood to the descending aorta. In Case 3 part of the blood in the descending aorta would seem to have come from the right ventricle and part through the lumen of the aortic coarctation, while in Case 4 wherein the aortic lumen was practically closed and the ductus arteriosus widely patent, it would seem that virtually all of the blood in the descending aorta was derived from the right ventricle. This concept is supported by the great degree of right ventricular hypertrophy present in both Cases 3 and 4.

The blood pressure in the lower extremities in Case 3 is not known. In Case 4 systolic pressure taken in the left leg varied from 98 to 102 and the diastolic ranged from 50 to 60 millimeters of mercury. These diastolic blood pressures compare rather closely with the blood pressures taken in the arms, which received their blood from the left ventricle. It is of interest that the right ventricular thickness was similar to, and even exceeded, that of the left ventricle.

If one assumes, as we are doing, that the right ventricle was responsible for the function of a systemic ventricle in addition to supplying the lungs, one would expect that the pulmonary vessels would exert resistance to blood flow of a magnitude which would equal or exceed that of the peripheral vessels. Otherwise flow of blood to the descending aorta from the right ventricle would not be possible. Moreover, one would have to assume that the resistance to pulmonary blood flow must have exceeded that to the peripheral flow from the time of birth. That vascular changes existed in the pulmonary arteries and arterioles, which narrowed the lumina of these vessels and created resistance to pulmonary blood flow, has been brought out in the text of this communication.

Just when these changes began to develop is impossible to state from an examination of the vessels. It is known that they were well established in Case 3, in which death occurred at 23 months of age. From our concept of the functional significance of these vascular changes, we assume that they may have started to develop before birth or very shortly thereafter.

In Case 4, in which there were intact cardiac septa, the right and left sides of the heart may be considered as separate functioning units. In Case 3 there was a ventricular septal defect through which the two ventricles were in communication. In this case the two ventricles might be considered as a single functioning unit.

Anatomic variations of the pulmonary arterioles similar to those observed in our Cases 3 and 4 might be expected in other cardiovascular malformations wherein a common source supplies blood to the pulmonary and the systemic circulations. Such malformations are persistent truncus arteriosus, cor triloculare biatriatum, and the Eisenmenger complex. Studies of the pulmonary vessels in these conditions are being carried out. Preliminary studies have indicated that the vascular changes are, indeed, similar to those in our Cases 3 and 4.

SUMMARY

This is a report of four cases wherein coarctation of the aorta and patent ductus arteriosus were associated. In two cases, in which the ages were 15 and 22 years, respectively, the coarctation was distal to the aortic mouth of the patent ductus arteriosus. In the other two cases, in which the ages were 23 months and 7 years, respectively, the aortic coarctation lay proximal to the aortic mouth of the ductus arteriosus.

Changes of significant proportions involved the intrapulmonary arteries and arterioles in each case. In the first two cases the changes were most striking in the intrapulmonary arteries. These consisted of medial hypertrophy, fragmentation of the elastic laminae, adventitial fibrosis, and fibrous proliferation of the intima. The changes were associated with significant degrees of narrowing of the arterial lumina. Thrombi in various stages of organization were encountered in both cases. In one case there was hyalinization of the intimal and medial tissue. The arterioles showed scattered changes of severe degree. In general, the arteriolar walls were thickened, a change associated with relatively narrow lumina. In one of the first two cases there was evidence that the right ventricle had exerted sufficient pressure to force blood into the aorta, thus assuming the function of a systemic ventricle.

In the second group of two cases the arteries of the lungs showed medial hypertrophy and adventitial fibrosis, changes associated with luminal narrowing. The arteriolar changes in these two cases were more striking than those in the first two cases. These changes likewise consisted of medial hypertrophy and adventitial fibrosis. In one case, in addition, intimal fibrous thickening of the arterioles was diffuse. In both of these cases the evidence suggested strongly that the descending aorta was supplied with blood by the right ventricle.

REFERENCES

1. Douglas, J. M., Burchell, H. B., Edwards, J. E., Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case With Obstructive Pulmonary Vascular Lesions, *Proc. Staff Meet., Mayo Clin.* **22**:413, 1947.
2. Parker, Frederic, Jr., and Weiss, Soma: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, *Am. J. Path.* **12**:573, 1936.
3. Patten, B. M.: *Human Embryology*, Philadelphia, 1946, The Blakiston Company, pp. 682-697.
4. Chapman, C. B., and Robbins, S. L.: Patent Ductus Arteriosus With Pulmonary Vascular Sclerosis and Cyanosis, *Ann. Int. Med.* **21**:312, 1944.

THE WATER TOLERANCE OF THE HYPERTENSIVE PATIENT. ITS RELATION TO OPERABILITY

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INTRODUCTION

IN PREVIOUS communications¹ we have stressed the importance of rigid selection of hypertensive patients for sympathectomy. The grading of the patients into three well-defined groups has been of definite value (Table I). That irreversible cerebral, cardiac, renal, or peripheral vascular damage vitiates the surgical results needs no further comment. It seems, however, that the functional state of the kidney, whether involved as a primary or a secondary factor in hypertension, needs closer attention. Clinical tests, readily performed in hospital laboratories, consist of the concentration-dilution test, the fifteen-minute phenolsulfonphthalein test, and the urea clearance test. Except in a few research institutions, the inulin and inulin-Diodrast clearance has not proved to be of practical applicability, although the recently simplified technique of Landowne and Alving² seems to be of definite promise. It occurred to us that the customary concentration-dilution test, which measures the extreme variations of concentration and dilution under simple clinically controllable circumstances, could be made more sensitive by collecting half-hourly samples during

TABLE I. THE THREE GROUPS OF ESSENTIAL HYPERTENSION

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|-----------------|--|
| <i>Group 1.</i> | Age below 40. Minimal or no detectable organic damage. Normal blood pressure on complete rest or barbiturates. Casual diastolic pressures above 100 millimeters of mercury. |
| <i>Group 2.</i> | Age from 20 to 55. Moderate vascular sclerosis in all organs. Well-demonstrable angiospasm. Diastolic pressures cannot be lowered below 110 mg. Hg by any method. Rising diastolic pressure during the course of last six months. |
| <i>Group 3.</i> | Large recurrent retinal hemorrhages and exudates or papilledema. High fixed diastolic pressure which cannot be lowered below 120 mm. of mercury. Congestive or anginal heart failure. Poor renal function. Numerous cerebrovascular accidents. An actual malignant or premalignant state of hypertension with continuous maximal angiospasm uninfluenced by either pressor or depressor stimuli. |
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Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

the period of dilution and testing them for volume and specific gravity. This is the water tolerance of Adelsberg and Fox,³ who applied it for the study of patients recovering from hepatitis.

In this communication we shall present different patterns of such tolerance curves, correlated with the hypertensive status and the postoperative course of one hundred patients. We shall then attempt to analyze the factors influencing such tolerance curves.

PROCEDURE

The patient receives nothing by mouth after 6 P.M. the night before. The bladder is emptied before the patient retires and the urine is discarded together with all other urine passed during the night. A specimen is requested at 8 A.M., after which 1,500 c.c. of water are consumed within one-half hour. No breakfast and no other liquid are permitted. Urinary samples are collected at half-hour intervals between 8 A.M. and 12 P.M. They are tested for volume and specific gravity. Obviously this is nothing but the customary concentration-dilution test except that volume and specific gravity are followed in half-hour samples. Normal subjects eliminate 1,200 to 1,500 c.c. of urine, with the peak in the first two hours; the specific gravity fluctuates inversely with the output (Fig. 1).

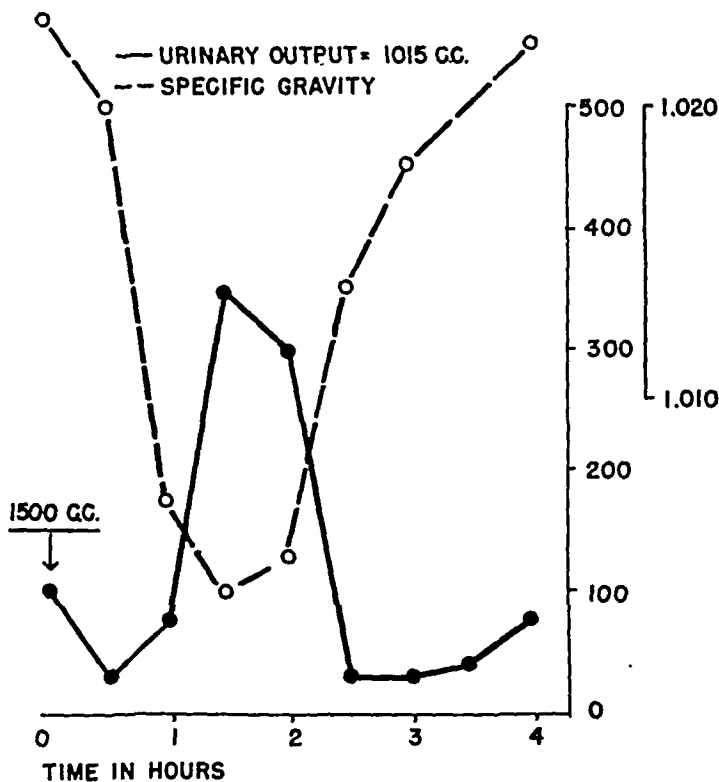


Fig. 1.—Water tolerance of Clare O., a 22-year-old man with normal cardiovascular status. Note the rapid return of specific gravity to a high level and the retention of ingested water, which seems to be a normal response of an individual restrained from drinking water for fourteen hours.

FACTORS INFLUENCING WATER TOLERANCE

We were anxious to know whether a weighed sodium and water intake prior to the test was necessary, and hence determined a few curves after sodium restriction and after excessive sodium and water intake. It did not seem that the normal individual was affected by these measures, but of course it is sufficiently known that the hypertensive individual tolerates salt restriction far better than the normal person.⁴ A water tolerance test indicating unusual sodium and water retention was only considered significant for corticoadrenal activity when the patient showed a decreased response to insulin, an abnormal sugar tolerance curve, or both.⁵ Such was the finding in the case of A. E., who had a left-sided corticoadrenal adenoma, proved by operation (Fig. 2). Desoxy-



Fig. 2.—Adenoma of the left adrenal cortex removed at operation.

corticosterone acetate has a similar effect on the curve of water excretion (Fig. 3).

An inhibition of diuresis is also accomplished by the *antidiuretic hormone of the pituitary*, whose secretion is inhibited whenever water is ingested. Such a curve is shown after the injection of 1.0 c.c. of Pitressin one-half hour before

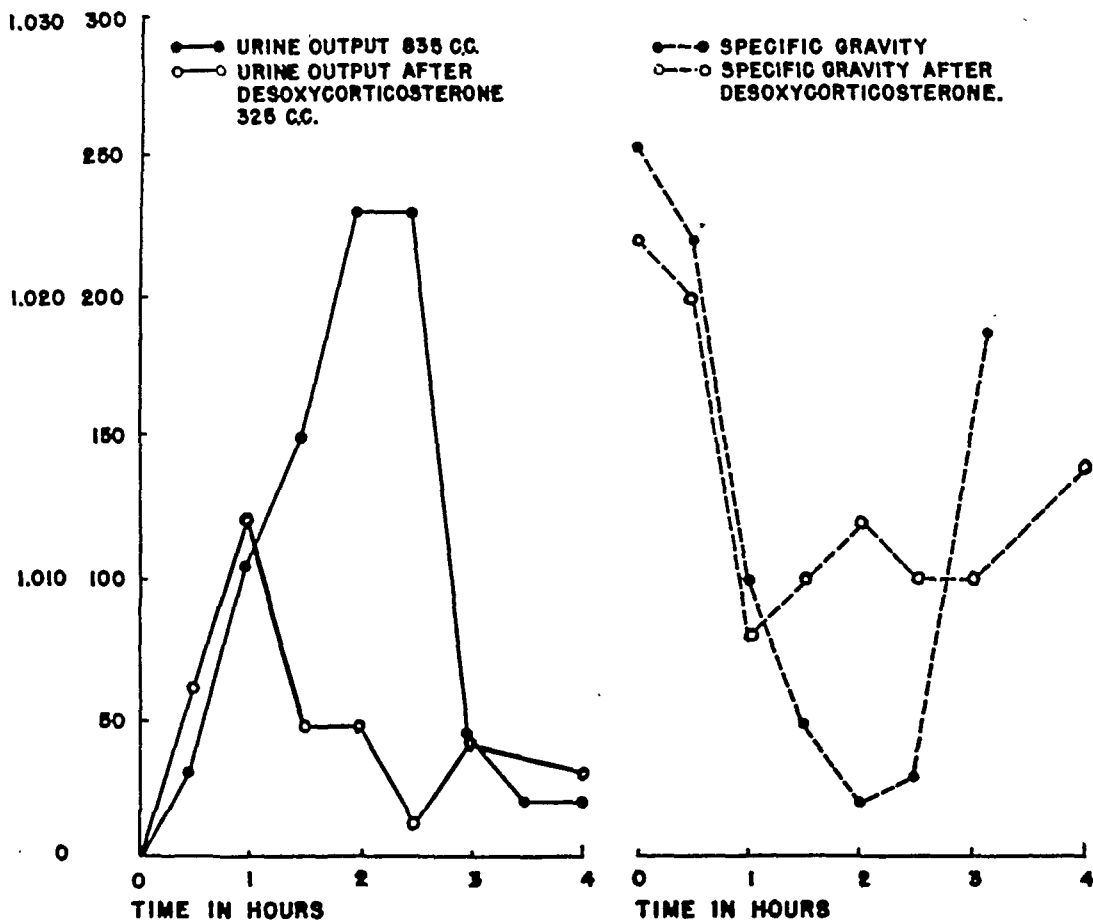
SPECIFIC URINE
GRAVITY IN C.C.

Fig. 3.—The effect of desoxycorticosterone acetate on water tolerance of Herman K.; 10 c.c. of this substance were injected intravenously the night before the tolerance was determined. Note the decrease in water excretion and the high specific gravity.

the water tolerance is started (Fig. 4). If a type of human hypertension exists which is mediated by the antidiuretic hormone, this should be demonstrable in the blood as Griffith and his associates⁶ have postulated for a certain group of patients. We have no experience with this method.

Water tolerance in *hepatic disease* has been studied by Adelsberg and Fox,³ who found significant changes in diuresis during different stages of liver disease. In the present group of patients hepatic damage could be excluded, with the exception of the middle-aged, alcoholic, atheromatous hypertensive persons, in whom we do not advocate operation. We finally come to the *renal factor*, which proved to be the most significant in this group of hypertensives who were studied for their operability. It has been our experience that of all the irreversible factors which are encountered in essential hypertension, the renal damage is most important, since, aside from the early vascular changes which may be on a functional basis and produce corticorenal ischemia,⁷ the fixed

vascular and parenchymal damage in the kidney seems to be least capable of improvement compared with the regression in the eye grounds, diminution in the size of the heart, or the changes in the electrocardiogram toward normal which follows splanchnicectomy.

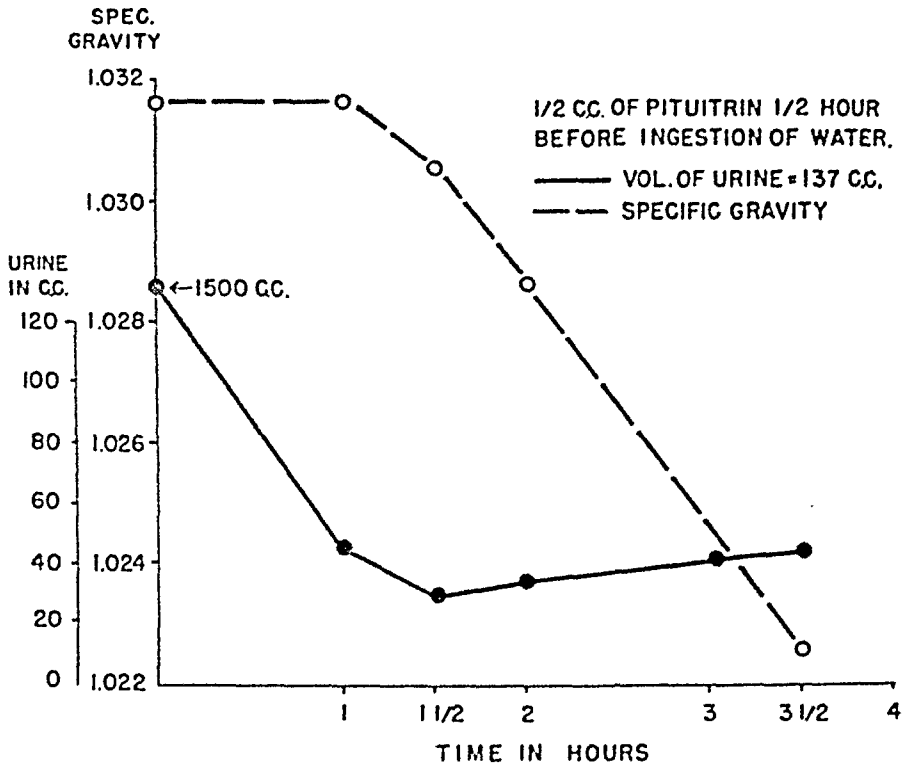


Fig. 4.—The effect of pituitrin on the water tolerance of Patrick K.

PATTERNS OF WATER TOLERANCE

From the standpoint of renal function, the concentration-dilution test has not been such a sensitive index as the water tolerance. The following six patterns have appeared after we have employed this test routinely for the past year in our preoperative studies in over one hundred patients.

Pattern 1.—(Janet J., Fig. 5.) This corresponds to the normal water tolerance as shown in Fig. 1. Fig. 5 illustrates this curve starting with a specific gravity of 1.015 which is regained in four hours. Water excretion occurs early, and after two hours not much urine is obtained. The urine showed no pathologic elements. The phenolsulfonphthalein excretion was always above 30 per cent and sometimes as high as 40 per cent in fifteen minutes. The urea clearance was above 40 c.c. per 100 c.c. of blood.

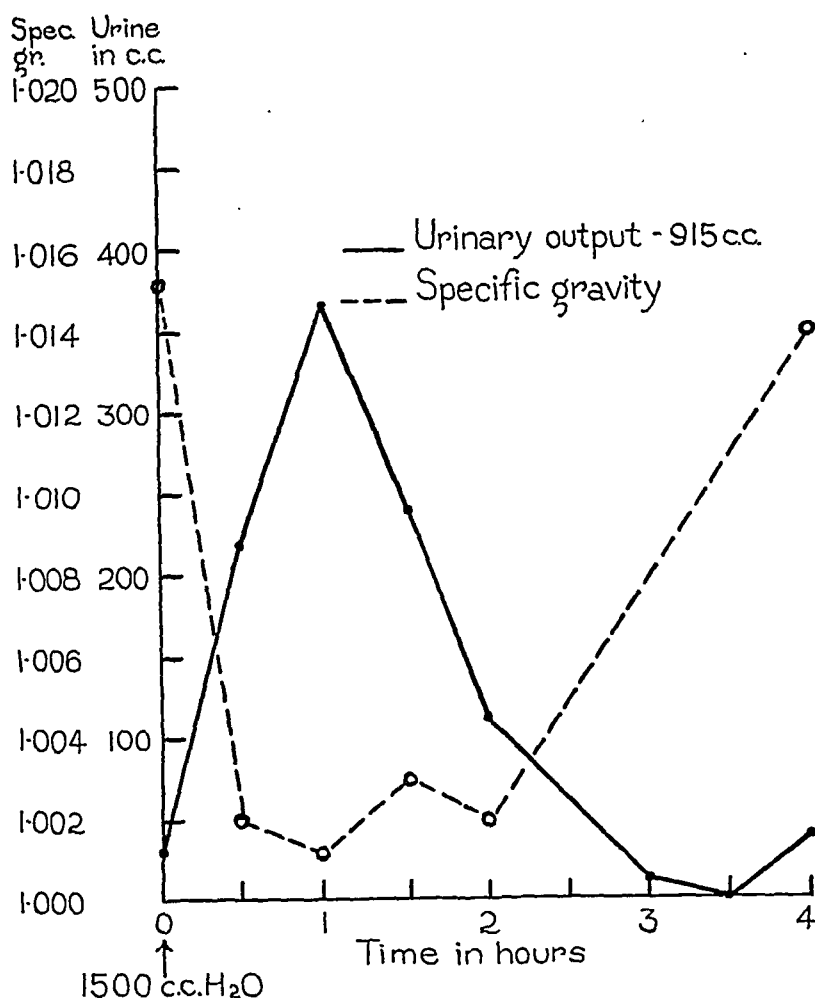


Fig. 5.—Water tolerance of Janet J., a 42-year-old married woman with Grade 2 hypertension. Duration of known hypertension, five years. Urine normal, fifteen-minute phenolsulfonphthalein excretion 30 per cent, urea clearance 42.7 cubic centimeters. Concentration-dilution, 1.015 to 1.001. Renal biopsy showed some replacement of parenchyma by fibrous tissue. Glomerular tufts showed cellular thickening and hyaline changes. Afferent arteriolar walls were slightly thickened. Lowest preoperative blood pressure 160/100. Postoperative blood pressure (thirty months follow-up) 120/80. Complete relief of symptoms.

Pattern 2.—(William L., Fig. 6.) From a specific gravity between 1.015 and 1.020 the curve drops to low figures and is only slightly regained. The ingested water is overexcreted. There is a considerable excretion of urine in the first two hours, and a plateau is not infrequent. The fifteen-minute phenolsulfonphthalein excretion in this group was just as high as in the first group, varying between 30 and 45 per cent. Their urea clearance was above 40 c.c. per 100 c.c. of blood standard clearance.

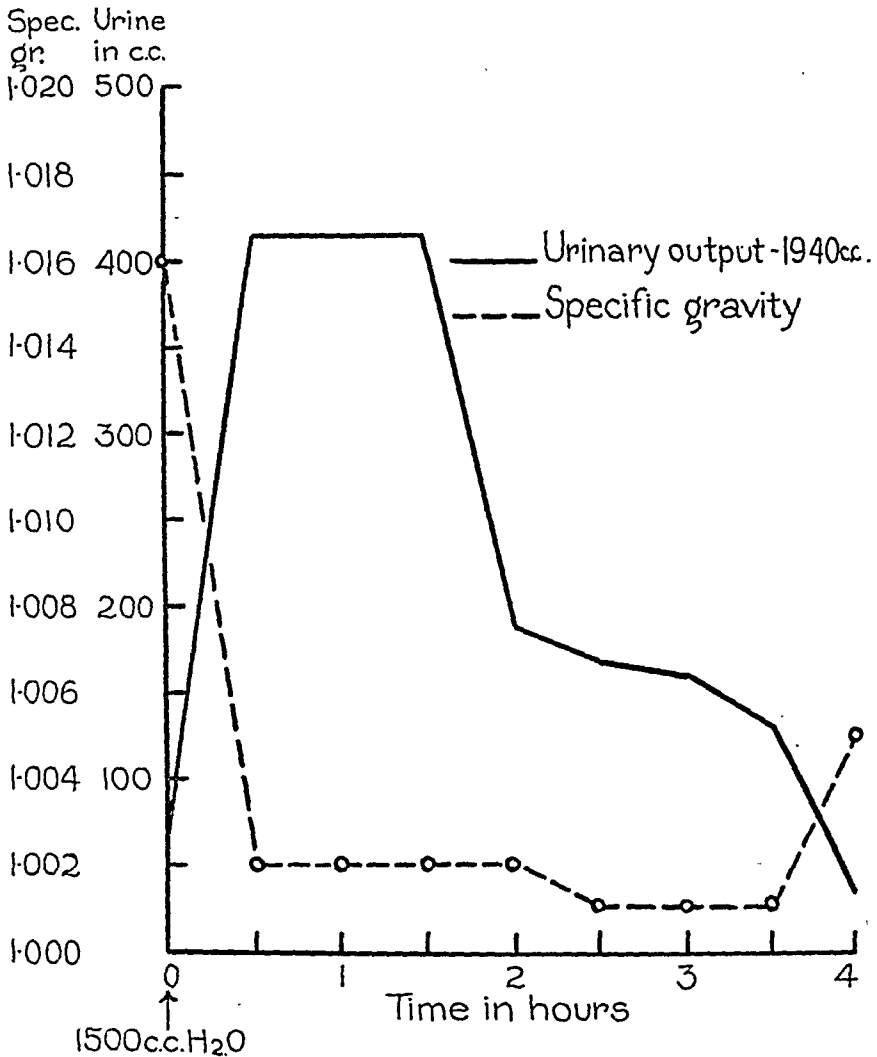


Fig. 6.—William L., a 49-year-old Grade 2 hypertensive man with a preoperative blood pressure of 220/130, a phenolsulfonphthalein excretion of 40 per cent in fifteen minutes, a urea clearance of 54 per cent, and concentration-dilution ranging from 1.016 to 1.002. However, he excreted the ingested water in four hours. Renal biopsy showed hyalinized glomeruli and increased cellular content of vascular tufts. Tubules contained granular precipitates. At discharge his blood pressure was 130/90 on lying down, with a pressure on standing of 70/0. Blood pressure after one year was 160/100.

Pattern 3.—(Edith D., Fig. 7.) This pattern starts with a high specific gravity, which drops and is hardly regained. Water excretion is definitely delayed, a shift to the right being obvious. Ingested water is overexcreted. Phenolsulfonphthalein excretion in fifteen minutes is still above 30 per cent and the urea clearance is widely fluctuating. Renal biopsies show more damage than in the previous groups.

Spec Urine
gr. in cc.

1.022 500

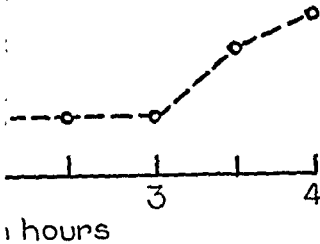
1.020

1.018 400

1.016

1.014 300

— Urinary output 1923 cc.
--- Specific gravity



housewife. Duration of known hypertension 1. Phenolsulfonphthalein (fifteen minutes) retention, 1.022 to 1.001. Renal biopsy showed glomerular hyalinization of the glomeruli, and thickening of the glomerular basement membrane as 260/140. Postoperative blood pressure

pattern starts with a fair concentration is maintained throughout. Water tolerance test over four hours. There is no overexcretion of phenolsulfonphthalein. Excretion of phenolsulfonphthalein excretion is maintained throughout. Renal biopsies show

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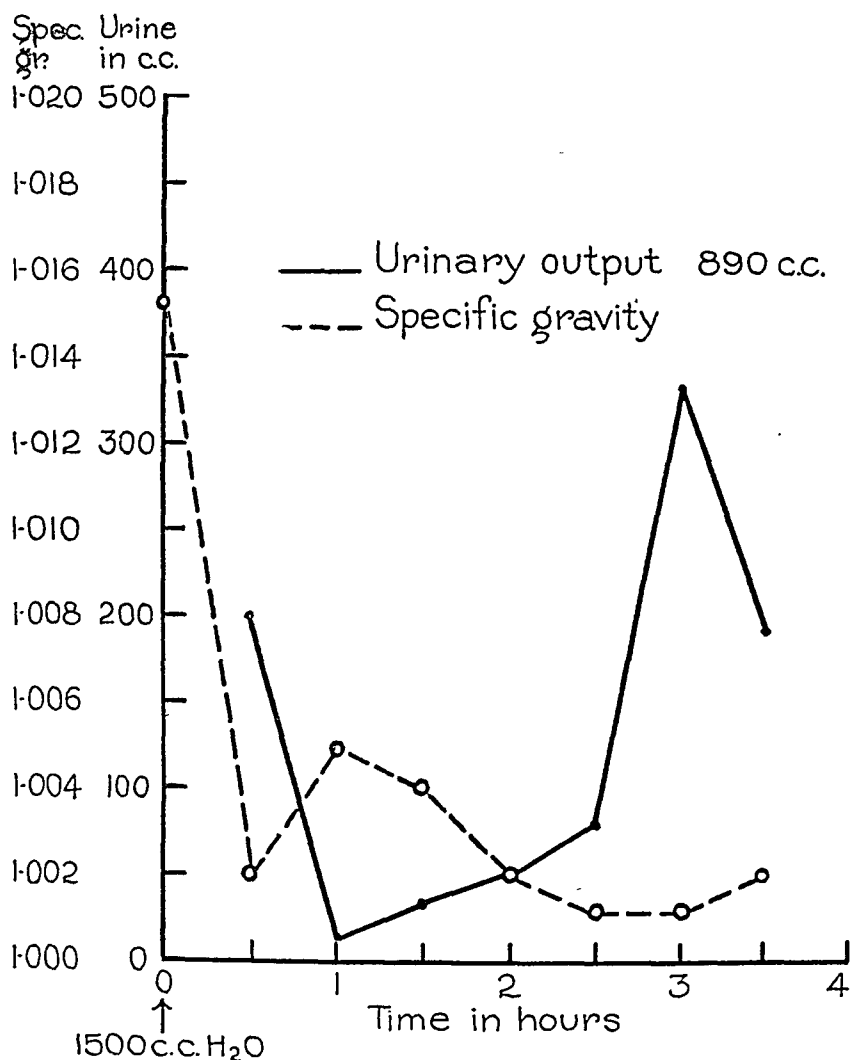


Fig. 8.—Florence H., a 52-year-old Grade 3 hypertensive woman, with a fifteen-minute phenol-sulfonphthalein excretion of 10 per cent, a urea clearance of 32 c.c., and a concentration-dilution of 1.015 to 1.001. Her preoperative blood pressure was 210/120. Biopsy showed a Grade 3 nephrosclerosis. Postoperative blood pressure was 190/110 six months later.

Pattern 5.—(James R., Fig. 9.) This pattern still shows a high concentration which promptly drops to a high dilution level, but never rises again.⁷ Water excretion starts after one hour, but is remarkably stable, the volume remaining fairly even throughout the four-hour period. The phenolsulfonphthalein excretion in fifteen minutes is below 20 per cent. This group shows evidence of advanced vascular sclerosis throughout the body.

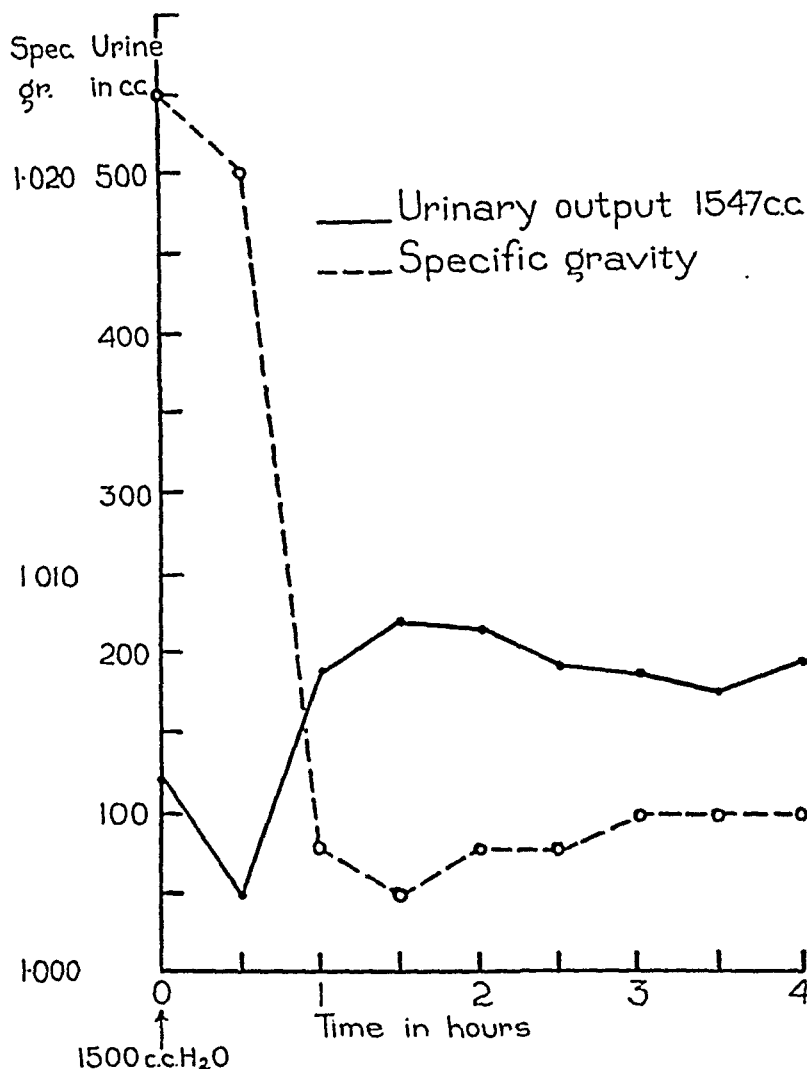


Fig. 9.—James R., a 56-year-old hypertensive man with a fixed arteriosclerotic hypertension, poor response to sodium amytal, and an excellent concentration-dilution test of 1.023 to 1.002. He was diagnosed as having an arteriosclerotic hypertension and was not regarded as a surgical case. He excreted the ingested water in four hours, but his urinary concentration remained low throughout the entire period.

Pattern 6.—(Lee L., Fig. 10.) This pattern shows high concentration, early reconcentration, and early water elimination. Both curves are highly unstable and a functional element affecting the renal vascular tree or excretory function is likely. Other renal function tests show no impairment of renal function. Such a curve may be stabilized by barbiturates or aminopyrin.

Other curves indicating a concentrating ability below 1.015 were not studied in detail since these obviously indicate advanced renal functional damage, a

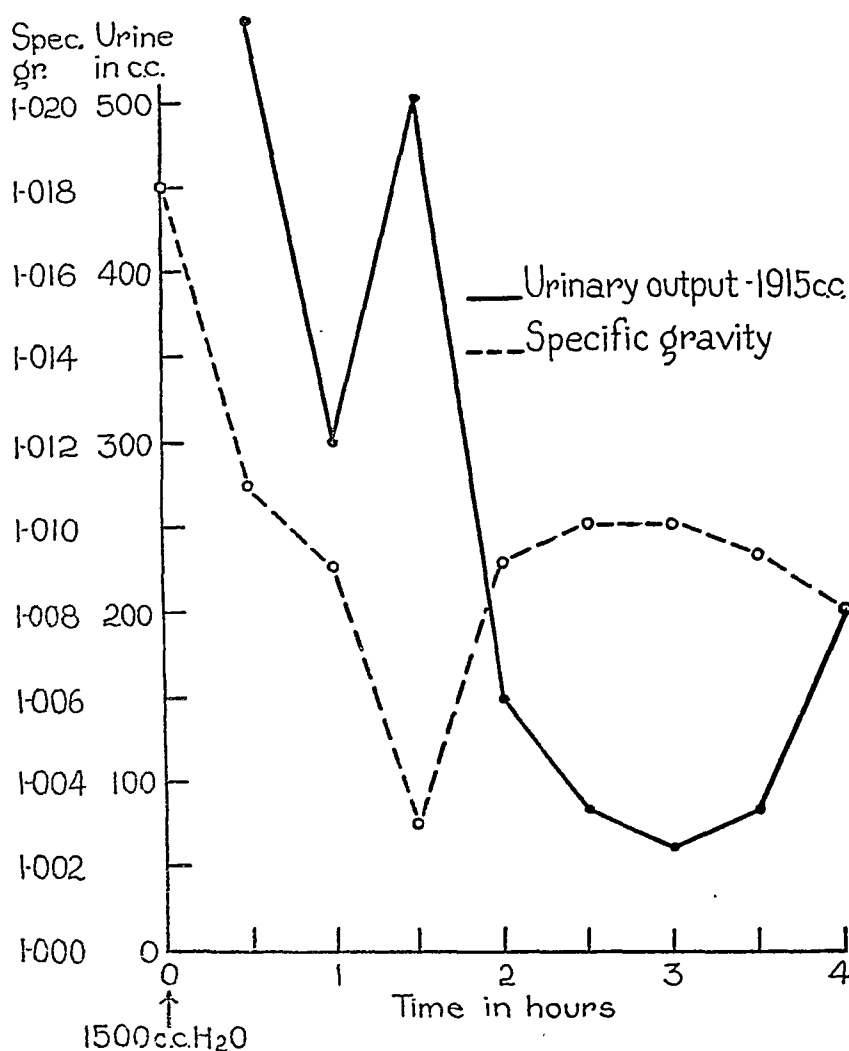


Fig. 10.—Lee L., a 49-year-old man with a Grade 2 hypertension. Duration of hypertension eight years. Urine normal, phenolsulfonphthalein excretion in 15 minutes 30 per cent. Urea clearance, 55 cubic centimeters. Concentration-dilution, 1.018 to 1.003. Renal biopsy showed moderate nephrosclerosis, Grade 1. Lowest preoperative blood pressure, 160/100; postoperative blood pressure (six months follow-up), 160/100 in the horizontal, 130/90 in the standing position. Note increased diuresis compensatory to incomplete reconcentration of urine.

hyposthenuria, or isosthenuria. However, to indicate the pattern of such a tolerance, we show the curve of Marian W. (Fig. 11), who showed a 10 per cent excretion of phenolsulfonphthalein in fifteen minutes, a fixed diastolic hypertension, and no visualization of the renal pelvis on intravenous Diodrast for a period of thirty minutes. Note the marked dilution, the overexcretion, and the complete failure to reconcentrate. This patient showed no response to splanchnicectomy, although an extended resection of the chain (D5 to L3) was done bilaterally.

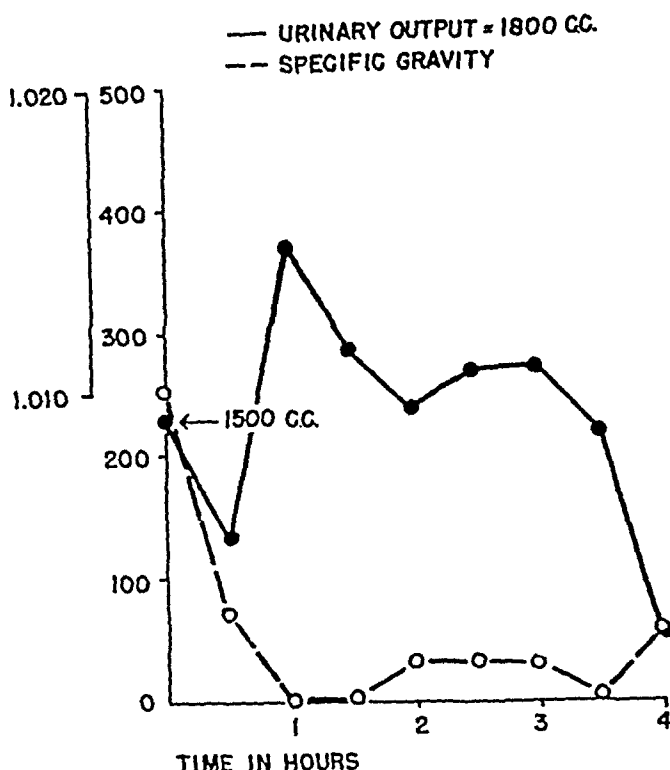


Fig. 11.—Marian W., a 34-year-old woman with a fixed diastolic hypertension between 130 and 140 mm. Hg and no visualization of the renal pelvis on intravenous Diodrast. Her fifteen-minute phenolsulfonphthalein excretion varied between 10 and 15 per cent. The urea clearance was within normal limits. Her blood chemistry was normal. The eye grounds and heart showed early (Grade 1) damage. Extensive splanchnicectomy failed to reduce her blood pressure.

THE CLINICAL SIGNIFICANCE OF THESE PATTERNS

The following table (Table II) shows the correlation of these patterns with the result obtained after sympathectomy. By failure we mean a rise of blood pressure within a year to the preoperative level. A good result is a diastolic

TABLE II. CORRELATION OF WATER TOLERANCE WITH RESULTS OBTAINED BY DORSOLUMBAR SYMPATHECTOMY

PATTERN	NUMBER OF CASES	RESULT		
		EXCELLENT	GOOD	FAILURE
1	15	13	2	—
2	42	3	39	—
3	29	—	21	8
4	9	—	1	8
5	*	*	*	*
6	5	—	5	—
Total	100	16	68	16

*No cases submitted to operation.

blood pressure stabilized between 100 and 110 mm. Hg when it was previously between 130 and 150 millimeters of mercury. An excellent result is a blood pressure below 140/90, at least one year after operation. A re-evaluation of the whole series after five years would no doubt give a smaller percentage of good results and we simply wish to illustrate a trend.

In the first two groups there were no failures and of course these belong to our intermittent or continuous but reversible stages of hypertension (Table III). The third pattern shows a great number of good results, but failures begin to occur. The fourth pattern with its failure to reconcentrate and a late water excretion has given very poor results, and the fifth pattern, since patients in this group exhibited advanced generalized arteriosclerosis, was not considered to be a surgical group. The significance of the sixth pattern is unclear and will be discussed.

TABLE III. EVOLUTION OF DIASTOLIC HYPERTENSION

<i>Reversible</i>	<i>Adolescent</i>	<i>Irreversible</i>
	<i>Intermittent</i> <i>Continuous</i> <i>Partly Reversible</i> <i>Malignant</i>	

DISCUSSION

Obviously no one test directed against a single organ can be of decisive influence regarding operability. Patients subjected to our preoperative study were examined regarding the functional status of their eye grounds, heart, peripheral circulation, and the flexibility of the vascular tree. Neither previous cerebrovascular nor coronary accidents were regarded as prohibitive indications, but advanced cerebral, cardiac, or peripheral vascular damage was regarded as prohibiting surgery. Added to this, failure to concentrate urine below 1.015 after fourteen hours of water deprivation, a fifteen-minute phenolsulfonphthalein excretion below 10 per cent of the dye, or a urea clearance of less than 20 c.c. per 100 c.c. of blood has been regarded as an argument against operation in the past.

In this series, however, we have found sixteen failures which do not fall into any of these categories. These operations were technically satisfactory and the general vascular damage was not advanced. Essentially they showed failure to reconcentrate urine in four hours, together with a late water excretion; the later the excretion, the more ominous the outlook. It should be emphasized that even Pattern 4 with one good result and eight failures shows no phenolsulfonphthalein excretion below 20 per cent in fifteen minutes and the urea clearance does not show consistent diminution below 50 per cent of normal. Ever since 1934 our group has accepted patients for splanchnicectomy with very restricted indications, and we now believe that the water tolerance test has given us one

more indication of irreversible renal damage, which neither renal nor adrenal denervation can alter. This group of sixteen patients showed a fair concentration-dilution test and would ordinarily be regarded as having sufficient renal reserve.

One cannot escape the conclusion that renal damage in hypertensive patients is more likely to be irreversible than cerebral or cardiac damage in spite of the fact that terminally renal failure is the least common cause of death. The vascular obliteration of the kidney may serve as a protective mechanism against progressive injury, but is at the same time uninfluenced by efforts of revascularization.

Patterns 5 and 6 are of special interest. Pattern 5 seems to represent the water elimination of a nephrosclerotic kidney with fixed renal function. On the other hand, Pattern 6 is certainly suggestive of emotional, neurovascular, or neurohormonal influences. Whether such a curve can be stabilized by sympathetic depressants or by central sedation is now under investigation.

SUMMARY

Normal water tolerance is defined as the ability of the individual to reconcentrate the urine during a period of four hours and to eliminate the ingested water mostly in the first two hours. Six patterns have been described which show response of the kidney to the ingestion of 1,500 c.c. of water. The patterns have been correlated with the results obtained in hypertensive patients following dorsolumbar sympathectomies. It seems that a certain group of failures could be avoided by excluding from surgery patients with crippled renal function. These patterns presumably indicate irreversible renal damage or such extra renal factors which sympathectomy does not influence.

REFERENCES

- 1 (a) De Takats, G., Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, *J. A. M. A.* 118:501, 1942.
(b) De Takats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: The Surgical Approach to Hypertension. Second Report, *Arch. Surg.* 53:111, 1946.
(c) De Takats, G., and Fowler, E. F.: The Surgical Treatment of Hypertension. III. The Neurogenic Versus Renal Hypertension From the Standpoint of Operability, *Surgery* 21:773, 1947.
(d) De Takats, G., Julian, O. C., and Fowler, E. F.: The Surgical Treatment of Hypertension. IV. Case Selection and Technique as Influencing Results, *Surgery* 29:469, 1948.
2. Landowne, M., and Alving, A. S.: A Method of Determining the Specific Renal Functions of Glomerular Filtration, Maximal Tubular Excretion (or Reabsorption) and Effective Blood Flow Using a Single Injection of a Single Substance, *J. Lab. & Clin. Med.* 32:931, 1947.
3. Adelsberg, D., and Fox, L. C.: The Changes of the Water Tolerance Test in Hepatic Disease, *Ann. Int. Med.* 19:642, 1943.
4. Perera, G. A., and Blood, D. W.: Disturbances in Salt and Water Metabolism in Hypertension, *Am. J. M. Sc.* 1:602, 1946.
5. De Takats, G.: The Cortico-Adrenal Factor in Hypertension, *Surgery*. In press.
6. Griffith, J. Q., Jr., Padis, N., and Anthony, E.: Selection of Patients With Arterial Hypertension for Treatment by Repeated Injection of Pitressin, *Am. J. M. Sc.* 212:31, 1946.
7. Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L.: Studies of the Renal Circulation, Springfield, Ill., 1947, Charles C Thomas, Publisher.

STUDIES ON PERIPHERAL CIRCULATION AND EPINEPHRINE SENSITIZATION FOLLOWING SYMPATHECTOMY

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WE HAVE reported elsewhere certain observations on the development of collateral circulation in dogs that had chronic femoral arteriovenous fistulas.^{1,2} Lumbar sympathetic ganglionectomy performed on the side on which the fistula was located resulted in a definite augmentation of the vascular bed in the corresponding limb, as demonstrated by angiography and measurement of cutaneous temperatures of the paw.

We also performed a series of acute experiments designed to determine whether there was a correlation of the rises in peripheral cutaneous temperatures following lumbar sympathectomy with direct measurements of peripheral arterial pressure and the blood flow in certain vessels of the limb. In addition, observations were made on the effects of intravenous administration of epinephrine in the sympathectomized and the normal limb.

THE EFFECTS OF SYMPATHECTOMY ON PERIPHERAL CUTANEOUS TEMPERATURE, ARTERIAL BLOOD FLOW, AND PRESSURE

Adult dogs weighing 17 to 19 kilograms were used in this study. The animals were anesthetized by intravenous administration of pentobarbital sodium (25 mg. per kilogram of body weight). Cutaneous temperature of the paws was taken with a thermometer having a thin glass mercury bulb. The surfaces of the toes were kept dry and shaved, and the air temperature was maintained at 26° Centigrade.

The left common carotid artery was cannulated and the mean arterial pressure was found to range from 120 to 170 mm. Hg as recorded by a mercury manometer. Both femoral arteries were exposed and ligated 2 cm. below the profundus branch. Cannulas were inserted into each femoral artery proximal to the ligatures and were connected to a mercury manometer. After control pressures in each femoral artery had been obtained (Fig. 1,a), the vessels were divided at the site of ligation. The cannulas were then introduced into the peripheral arterial stumps to permit determination of the pressure and blood flow of the peripheral arterial or retrograde collateral circulation. Blood obtained from the femoral arterial cannulas during each direct measurement of blood flow was immediately returned to the circulation by way of a cannulated jugular vein.

Since the lumbar sympathectomy was to be carried out transabdominally, laparotomy was performed early in the experiment to minimize the loss of blood following the administration of heparin, which was required for the experiment. At the completion of the cannulations and the laparotomy, 1,200 units of heparin were given intravenously, and 50 c.c. of a 1 to 100 solution of heparin in isotonic sodium chloride was injected by way of the jugular cannula every thirty minutes thereafter.

The following results were obtained immediately before and immediately after sympathectomy:

Results.—

A. Cutaneous Temperatures: The temperatures of both feet paralleled each other during the period before sympathectomy. Differences of 0.5 to 1.0° C. continued throughout the experiment if they were present initially. The anesthesia caused a transient rise from the control value of 31.5 to 35.0° Centigrade. The bilateral ligation of the femoral arteries just distal to the profundus branches, at the time of the cannulations, caused a rapid drop of temperature in each foot of 1.0 to 1.5° Centigrade. The temperature of the control limb then averaged 31.5 to 32.0° C. for the remainder of the experiment. After unilateral lumbar sympathetic ganglionectomy, the foot on that side became warmer at once, with a rise in temperature of 3.0° C., whereas the control side remained unchanged or became 0.5° C. cooler. This increase of cutaneous temperature on the sympathectomized side persisted throughout the period of observation.

B. Arterial Blood Flow: After the animal had been heparinized, blood flow was measured in cubic centimeters per minute directly from a T tube attached to the cannulas in the distal stumps of the femoral arteries. [Five minutes after cannulation, the blood flow averaged 75 c.c. per minute from each side. In agreement with the findings of Eckstein, Gregg, and Pritchard,³ there was a gradual increase of this flow, possibly as a result of a decrease of the peripheral resistance and an increased number of functioning vessels forming the collateral bed. After twenty to thirty minutes, the blood flow from each side was about 85 c.c. per minute, and it remained relatively constant for the subsequent observations.

Left lumbar sympathectomy was performed and immediately the retrograde blood flow from the peripheral arteries of that leg rose to 100 c.c. per minute, reaching 120 c.c. per minute in thirty minutes. This increase over control values amounted to about 40 per cent. [In the control limb, the figure of 85 c.c. per minute was maintained, or reduced slightly, after contralateral sympathectomy. When a decrease of flow was observed in the control limb, there was also observed concurrently a decrease of cutaneous temperature and an increase of peripheral blood pressure.

In one experiment the continuity of the femoral arteries was re-established bilaterally by means of cannulas after sympathectomy had been performed. An increase of blood flow of 100 per cent in the sympathectomized limb over the control limb was measured from the femoral veins after cannulation. The

fact that the augmentation following sympathectomy was greater from the veins than from the retrograde arterial outflow may be explained on the basis of the difference in capacity of the arterial beds represented by each of these measurements.

The increased flow of blood following sympathectomy in all of these experiments lends support to the belief that this procedure should be expected to augment the collateral circulation of a limb after the occlusion of a major artery.

C. Peripheral (Retrograde) Arterial Pressure: Control pressures in the intact femoral arteries generally ranged between 145 and 155 mm. of mercury (Fig. 1,a). Subsequent mean arterial pressures were measured by mercury manometers from the cannulated peripheral stumps of the femoral arteries. Immediately after ligation of the femoral arteries, the retrograde blood pressures averaged 75 mm. Hg, or about 50 per cent of the systemic pressure (Fig. 1,b). There was an increase to 80 or 85 mm. Hg during the next fifteen to thirty minutes.

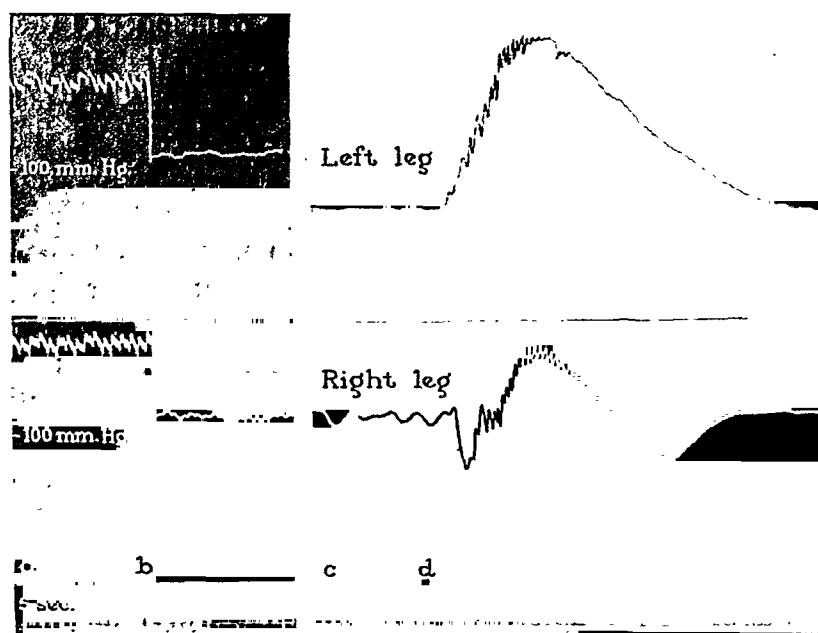


Fig. 1.—Effect of epinephrine after lumbar sympathectomy. *a*, Systemic arterial blood pressure obtained from both femoral arteries by direct measurement with a mercury manometer. *b*, Peripheral arterial blood pressure obtained from the distal stump of each femoral artery divided below the profundus branches. *c*, Peripheral pressures of each femoral artery immediately after left lumbar sympathectomy. Note the fall of pressure on the sympathectomized side, with a loss of vasomotor fluctuation. *d*, Intravenous injection of 0.05 c.c. of 1:1,000 solution of epinephrine thirty minutes after sympathectomy. Note the greater rise of blood pressure on the sympathectomized side and the longer duration of the increased blood pressure.

After sympathectomy, the retrograde arterial pressure on the ipsilateral side decreased at once to 60 to 65 mm. Hg, indicating the removal of a definite degree of peripheral resistance (Fig. 1,c). The unsympathectomized limb occasionally showed an increase of pressure of 5 mm. of mercury. The sympa-

thetic denervation deprived the affected vascular bed of its normal dynamic vasomotor fluctuations (compare in Fig. 1 the segment *c-d* of the left leg with that of the right).

Comment.—The results of these studies are in agreement with those of previous investigations, which demonstrated that an acute obstruction to a major arterial channel results in an immediate decrease of peripheral cutaneous temperatures, arterial flow, and arterial pressure. There soon follows a rapid, progressive rise of cutaneous temperature, blood flow, and arterial pressure distal to the occlusion, which might reasonably be interpreted as the result of improved collateral circulation, as observed after occlusion of the femoral, carotid, and coronary arteries of dogs.³ We recognize that very rigid control must be kept over the many possible variables accompanying the measurement of cutaneous temperature if significance is to be given to the data obtained.⁴ In previous studies we employed both galvanometric thermocouples and chemical thermometers, but, for convenience, in this series of experiments we employed only the thermometer. The data on cutaneous temperature that we obtained with the animals in a relatively constant environment showed a close correlation with the data obtained on arterial blood flow.

Our results varied in certain particulars from those of Theis,⁵ whose methods of procedure we employed in general. Whereas we noted a consistent fall of about 25 per cent in the peripheral arterial pressure following sympathectomy (Fig. 1,*c*), Theis obtained a rise of 15 per cent, which he explained on the theory of an increase of blood flow. We accounted for our results on the theory that the decrease of the peripheral resistance resulting from sympathectomy exerted a greater influence on arterial pressure than did the increase of blood flow.

Similarly, Smithwick,⁶ in reviewing 156 cases after thoracolumbar sympathectomy and splanchnicectomy for hypertension, found no drop of systemic blood pressure in only 9.7 per cent, with a decided decrease of pressure in more than 80 per cent of the cases. Leriche and Fontaine,⁷ as well as Frier and Nassi,⁸ demonstrated a persistent drop of the peripheral arterial pressure of dogs following a fleeting rise after block or extirpation of the lumbar sympathetic ganglia.

We found a 40 per cent increase of retrograde arterial blood flow following sympathectomy, as compared to 60 per cent reported by Theis. In our studies, the animals were heparinized and cannulas were used for the measurement of blood flow. The determination of collateral arterial blood flow by direct measurement from the peripheral stump of the artery leaves much to be desired, but it was the most unequivocal method available to us at the time.

HYPERACTIVITY OF DENERVATED BLOOD VESSELS TO EPINEPHRINE

In addition to the experiments just described, studies were made of the hyperactivity of denervated blood vessels to epinephrine following sympathectomy. Increased response of smooth muscle to epinephrine following such denervation has been the source of some disagreement since the phenomenon

was first described by Meltzer and Meltzer⁹ in 1903. Although most workers agree that both preganglionic and postganglionic division of the fibers will result in hypersensitivity, postganglionic division usually is considered much more effective in this respect. However, there is not complete agreement on this point. Furthermore, there has not been agreement concerning the time at which the hypersensitivity to epinephrine begins to appear. While many of the reports on sensitivity to epinephrine do not refer to a specific time of onset, those which do consider this aspect of the problem may be divided into two groups: first, those which refer to an immediate difference in the response of a sympathectomized part to epinephrine; and second, those which indicate a variable period following the denervation during which evidence of sensitization was not observed. This latter group included certain studies in which the observations were apparently not begun until several days after the denervation.

It was not our original intention to study this interesting problem, since our primary concern was with the behavior of the collateral circulation associated with a chronic arteriovenous fistula. However, during the acute experiments already described in this paper, intravenous injections of epinephrine were followed by such significant differences in the response of the sympathectomized limb as compared to the control limb that additional experiments were subsequently done.

Results.—

A. Retrograde Arterial Blood Flow and Peripheral Pressure: In three of the dogs already described in this paper, 0.05 mg. of epinephrine hydrochloride was injected intravenously thirty and sixty minutes after unilateral lumbar sympathectomy.

The retrograde arterial blood flow increased on both sides in response to epinephrine, but it was much greater on the sympathectomized than on the control side. It averaged 160 c.c. per minute on the sympathectomized side and 130 c.c. per minute on the control side, as compared with initial values of 120 c.c. per minute and 85 c.c. per minute, respectively.

The peripheral arterial pressure likewise rose on both sides. The blood pressure on the control side reached 180 mm. of mercury, while on the sympathectomized side it reached 230 mm., as compared to the control values of 90 mm. and 65 mm., respectively. The arterial pressure curve differed markedly on the two sides. The control side first showed a slight or moderate fall of blood pressure, which was immediately followed by a marked rise lasting one minute. The pressure then decreased from the peak to less than the control level, and recovered in twenty seconds. On the sympathectomized side, the pressure curve rose immediately from the base line to a higher peak, and decreased slowly to the base line, the entire elevation lasting three minutes (Fig. 1,d).

B. Blood Pressure in Uninterrupted Arteries: In three large adult dogs, after laparotomy and heparinization, the femoral arteries were exposed. Instead of interrupting the femoral arteries, we inserted special T tubes into them immediately below the profundus branches. These T tubes had an in-

side diameter of 2 mm., and were coated with silicone* to retard clotting. Mercury manometers were connected to each T tube for simultaneous recording of the lateral arterial pressures of both femoral arteries. A control tracing was also made from the left carotid artery in each instance. Fresh solutions of epinephrine hydrochloride were injected intravenously, recovery being allowed to occur between doses. The dose used throughout this experiment was 0.05 milligram.

After left lumbar sympathetic ganglionectomy it was interesting to note that a difference in the lateral pressures of the femoral arteries in response to the epinephrine was not apparent when the arterial continuity was intact. The femoral arteries were then occluded temporarily with Carrel clamps immediately proximal to the T tubes. Injections of epinephrine then caused a marked increase of height and duration of blood pressure (similar to that shown in Fig. 1,d,) in the sympathectomized limb over that occurring in the control limb, in all instances. When the clamps were removed and continuity of the vessels was re-established, there was again no difference of response to epinephrine in the two limbs.

Right lumbar sympathetic ganglionectomy was then performed. With the T tubes unobstructed there was again no difference in the response of either leg to the solutions of epinephrine. The pressure curves corresponded to those obtained in the control period prior to the sympathectomies. Carrel clamps were again placed proximal to the T tubes. The height and duration of both pressure curves following injection of epinephrine coincided, but were much greater than had occurred with the T tubes open.

Comment on Sections A and B.—It was interesting to note the increase of direct flow which followed the injection of epinephrine. Previous studies in this laboratory, in which flow was measured by the thermostromuhr in vessels of dogs several months after sympathectomy, had indicated that a marked decrease of flow occurred with an injection of epinephrine. The present studies were performed immediately after the sympathectomy, and utilized the distal stump of the severed femoral artery. Since retrograde arterial outflow from the stump was more easily effected by the blood in the anastomosing collateral arteries than by passage through the distal constricted arteriolar bed, this measurement cannot be compared with those on an intact vascular bed. The one salient point from both types of study is that there is a significant difference in the response of the sympathectomized side, be it a matter of minutes or months after the operation.

The significance of the recorded difference in the arterial pressure between the control and the sympathectomized limb in these experiments lies in the fact that hyperreactivity to epinephrine was demonstrated within a few minutes after the denervation. Some authors, among them Elliott,¹⁰ Freeman and his associates,¹¹ and Smithwick and his associates,¹² have maintained that sensitization of denervated vessels to epinephrine is not present for about a week after sympathetic denervation.

*A product of General Electric Company (Dryfilm).

A number of variables have made a clear understanding of this problem more difficult. Meltzer noted immediate differences in response to epinephrine while he was observing the blood vessels in the rabbit's ear after removal of the superior cervical ganglion, whereas twenty-four hours were needed for the demonstration of similar differences when the iris muscle was studied in the rabbit. In similar experiments performed on the cat's eye, a lag of forty-eight hours was observed.^{13,14} The nictitating membrane of the cat and the hand of the monkey and man have been employed as test organs also. Direct observation and recorded measurements of blood flow, surface temperature, arterial pressure, and strength of contraction of smooth muscle have been various means of demonstrating differences of response to epinephrine (Table I). As has been indicated earlier, our previous experiments concerned the development of collateral circulation in the dog, and consequently this animal was used for the present experiments, attention being directed primarily to the vascular system.

C. Venous Outflow: During the course of these experiments we were interested in the response to epinephrine, before and after sympathectomy, of the blood flow and pressure in the femoral veins with intact arteries. Accordingly, our initial study was made of the venous outflow. Both femoral veins were exposed and, after division distal to the profundus branches, the peripheral stumps were cannulated. In heparinized and anesthetized dogs weighing 5 to 7 kilograms the control blood flow, measured directly, averaged 12 c.c. per minute. With each injection of 0.01 c.c. of a 1 to 1,000 solution of epinephrine per kilogram of body weight, there appeared an immediate brief increase of outflow, to 15 c.c. per minute. This was swiftly followed by a diminution of outflow to a level of about 8 c.c. per minute. This outflow represents free continuous outflow from the cannula, during a period in which the blood was measured at intervals of one minute and was then slowly returned continuously by the jugular cannula. There was no muscular activity nor alteration of posture during the measurements, since these studies were carried out on animals anesthetized by intravenous administration of pentobarbital sodium (25 to 30 mg. per kilogram).

D. Venous Pressure: Three dogs were then used for a similar study of venous pressures in the intact vein. The femoral veins were exposed and a vertical slit was made in the the wall of each vein 1.0 cm. below the profundus branches. Glass T tubes, coated with silicone, were inserted into the lumen of the vein. The upright arm of the T tube was fitted to a straight vertical glass tube of the same diameter. This tubing, which had been filled with a 1 to 100 solution of heparin, then constituted a direct pressure manometer. The dogs which had been heparinized were given graded doses of epinephrine, with time for recovery between injections. A constant response occurred in the systemic arterial pressure, as recorded from the carotid artery, for each dose of epinephrine. Doses of 0.001 mg. per kilogram and 0.0001 mg. per kilogram were the usual amounts injected intravenously. The arterial pressures recorded for these doses were 170 and 135 mm. Hg, respectively, from a control level of 115 mm. of mercury. The control venous pressures for both

TABLE I. RESPONSE OF SYMPATHECTOMIZED ANIMALS TO ADMINISTRATION OF EPINEPHRINE

DATE	AUTHOR	POSTGANGLIONIC OR PREGANGLIONIC SYMPATHECTOMY	METHOD AND ORGAN	ANIMAL	RESULTS
1903	Meltzer and Meltzer ⁹	Post-	Blood vessel of ear	Rabbit	Immediate
1904	Meltzer and Auer ¹³	Post-	Pupil	Rabbit	Need 24 hours
1904	Meltzer ¹¹	Post-	Pupil	Cat	Need 48 hours; still present 3½ months
1905	Elliot ¹⁰		Innervation by sympathetic, all organs		Need 1 to 2 weeks
1918	Dale and Richards ¹⁵	Post-	Leg: B.P. and plethysmograph	Cat	Epinephrine and histamine immediately, better later; present at 26 days
1932	Rosenbleuth and Cannon ¹⁶	Post-	Nicotinating membrane	Cat	Good effect noted after 4 to 5 days
1932	Daniélopou and others ¹⁷	Post-	Leg	Man	Noted sensitivity with unilateral sympathectomy
1934	Freeman and others ¹¹	Post-	Digits (alcohol injection)	Man	No temperature drop second to sixth day
			Paw	Cat	Noted on eighth, also eighteenth
			Ear	Rabbit	
			Used 1:250,000 or 0.0001 to 0.0003 mg./kg./min.		
1934	Smithwick and others ¹²	Post-	Like Freeman and others		Nothing first week
			maximal drop 15° F.		
1935	Grant ¹⁸	Post-Pre-	Ear	Rabbit	Increased during 5 to 7 days; constant up to 15 months; post- more than pre-
1935	Hampell ¹⁹	Post-Pre-	Nicotating membrane 1:50,000; 1:1,000,000	Cat	Rapid increase during 6 to 8 days, less in next week; maximum at 14 to 15 days
1936	White and others ²⁰	Post-Pre-	Hand	Monkey	Slow increase for days
			Ear	Rabbit	Maximum in second week; post- 2 to 3 times more than pre-
1937	Ascroft ²¹	Post-Pre-		Monkey	Post: epinephrine sensitization increased 10 times pre: epinephrine sensitization increased 3 times
1938	Fatherree and Allen ²²	Post-	Digits	Man	Criticism of temperature
1940	Fatherree and others ²³	5 post-8 pre-Review	Digits	Man	Pre- 2 times post-; feel site more important than pre- or post-
1946	Grimson ²⁴				Sensitivity develops rapidly but does not reach peak until within second week; persists unless regeneration occurs
1947	Deterling and Essex	Post-Pre-	Kidneys Paw	Dog Dog	Immediate effect Immediate effect

CASE 143.—A 63-year-old woman was brought to the hospital in coma complicated by profound circulatory collapse. No further history was obtainable. Death occurred one hour after admission. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained one-half hour after admission is reproduced in Fig. 5, B. Interference dissociation was present with an atrial rate of 70 and a regular ventricular rate of 90 per minute. The ventricular complexes were uniform in any given lead and thus arose from a single focus. The following interpretation was based on the supposition of a nodal, rather than idioventricular, pacemaker. The duration of the QRS complex was 0.12 second and abnormal slurring or notching was present in every lead except V_3 . An initial Q wave was recorded in Leads V_1 , V_2 , and V_4 , but was absent from most cycles of Lead V_3 , probably because the first portion of the QRS complex was isoelectric in this lead. This assumption was supported by the fact that the measurable QRS duration in V_3 was only 0.08 second, as compared with 0.12 second in leads to the right and left. The Q wave of Lead V_1 was followed by a notched upstroke, late intrinsicoid deflection, elevated RS-T junction, and coved inversion of the T wave. Lead aV_R also displayed a Q wave, prominent late R wave, elevated RS-T junction, and deeply inverted T wave. The findings in Leads V_1 and aV_R were subject to two widely divergent explanations: (1) anteroapical infarction, involving enough of the septum to produce the pattern of right bundle branch block in Leads V_1 and aV_R and continuing sufficiently into the subendocardial portion of the anterior wall to account for the Q wave in Lead V_4 ; (2) rotation of the heart, so that the potential variations of the posterobasal aspect of the left ventricle were transmitted to the right arm and carried through to the right anterior chest wall to produce the QR pattern in V_1 . It was difficult to reconcile the second alternative with the fact that the transitional zone was apparently near the midline anteriorly and the potential variations of the anterior and lateral walls of the left ventricle were referred to precordial Positions 2 to 6, inclusive. This would have meant that the potential variations of some portion of the epicardial surface of the left ventricle would have been referred around the entire circumference of the chest, which was anatomically implausible. Hence, the first alternative was favored. The pattern in Leads V_2 and V_3 was subject to slight cyclic variation, a minute initial Q wave usually being present in V_2 and absent from V_3 , but in a minority of cycles the Q wave was absent from V_2 and present in V_3 . A Q wave was consistently present in Lead V_4 and varied from 2.0 to 4.0 mm. in depth and from 5 to 10 per cent of the amplitude of the succeeding R wave. Despite the low Q/R ratio, the Q wave was considered abnormal because of its coarse slurring and because of the 0.04 second interval from its onset to nadir. This, together with the RS-T elevation and T-wave inversion, pointed to a recent patchy infarct. Leads V_5 and V_6 showed an initial upstroke that was abnormally slurred and prolonged. The pattern in Lead aV_L , on the other hand, resembled that of V_4 and, along with the findings in the first four precordial leads, suggested infarction of the subendocardial layer of the basal portion of the anterolateral wall. The Q wave of aV_L was obliterated in Lead I because of the simultaneous greater negativity of the right arm. Death occurred before additional high precordial leads could be taken.

Pathologic Findings.—The heart weighed 341 grams and exhibited a calcareous aortic stenosis. By means of multiple microscopic blocks encircling the ventricle, an acute subendocardial infarct was found localized to the areas demarcated by the solid line in Fig. 7. This infarct involved the lateral wall at the base and extended diagonally forward into the anterior wall near the apex, but spared the septum and right ventricle. It apparently had occurred as a terminal event secondary to the peripheral circulator collapse consequent upon cerebral hemorrhage, which was the primary cause of death. The involvement of the anterior wall near the apex was probably responsible for the pattern in V_4 , and the high lateral part of the infarct may have accounted for the findings in Lead aV_L . In view of the counterclockwise cardiac rotation and displacement of the transitional zone to the right, the infarction of the subendocardial layer of the anterolateral wall in the basal segment may have been responsible for the QR pattern in Leads V_1 and V_2 . Since the electrocardiogram was obtained shortly before death, the bizarre findings may have reflected terminal functional changes independent of the demonstrated anatomical lesions.

were noted on the control records and were found to correspond to fluctuations in the record of the systemic arterial pressure. With a control dose of 0.05 c.c. of a 1 to 1,000 solution of epinephrine, the carotid arterial pressure rose from 110 mm. Hg to a peak of 210 mm. of mercury. Both kidneys showed a concomitant decrease in volume of an identical degree (Fig. 2,*a*). The left kidney was then denervated of sympathetic fibers, with no alteration in systemic pressure (marked by arrow in Fig. 2). Epinephrine in the same dosage was given immediately after this denervation. Whereas the response of the right kidney was of the same magnitude as before, that of the denervated left kidney was much greater. The decrease of the volume of this organ was greater than before denervation, and was of longer duration (Fig. 2,*b*).

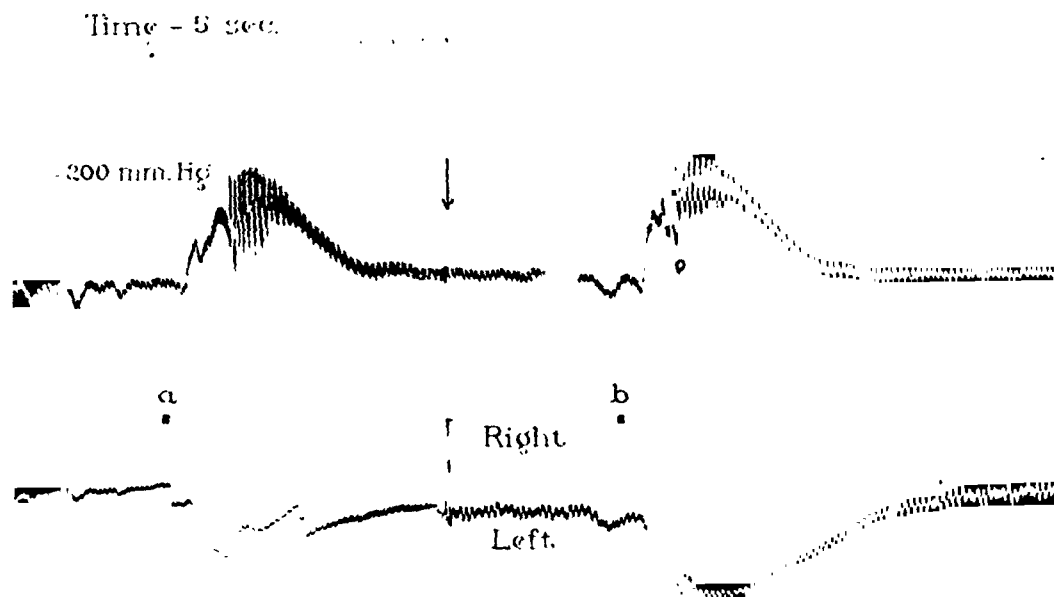


Fig. 2.—Effect of epinephrine after renal denervation. Above the base line, the systemic blood pressure is recorded by a mercury manometer from the carotid artery. Below are the plethysmographic records from the right and left kidneys. *a*, Response to 0.05 c.c. of 1:1,000 solution of epinephrine. Arrow marks the denervation of the left kidney. *b*, Response to the same dose of epinephrine after the denervation. Note the greater decrease in size of the denervated organ, and the longer duration of the effect as compared with the control side.

Comment on Section E.—Denervation of a kidney involved postganglionic denervation, in contrast to the preganglionic denervation carried out in our studies of the hind limbs. Nevertheless, we noted an excessive response to epinephrine immediately after denervation in *both* instances, even though different organs and different methods of measurement were employed.

Various hypotheses have been proposed to explain the phenomenon of epinephrine sensitization.^{19,20,24} Cannon and Bacq thought that denervation permitted an accumulation of sympathin in the idle cells. When touched off by an effective stimulus, there was an excess of sympathin to react with epinephrine. Bacq later altered his ideas and claimed that the production of sympathin ceased with a detoxication of the cells. This in turn resulted in a lowered

threshold to sympathomimetic polyphenols. Rosenbleuth and Cannon¹⁶ subsequently stated that an increased permeability of the cell occurs as a result of denervation or application of cocaine. This has had support in the work of Alpern and Gabbe. Ascroft,²¹ in support of Feldberg and Gaddum, found sensitivity to acetylcholine in decentralized ganglia. He expressed the belief that sensitization to epinephrine occurred as a change in or near vessels after denervation, resulting perhaps in a retardation of oxidation of epinephrine.

There have been those who maintained that degeneration of the vasomotor nerves must occur before such hypersensitivity can be detected. Smithwick, Freeman, and White¹² supported this view, and stated that sensitization was "not present after procaine hydrochloride block or during the first week after operation. We have found that it takes from seven to eight days for sensitization to appear."

These experiments clearly indicate that, as demonstrated by the methods used in this investigation, hypersensitization may occur *immediately* after preganglionic or postganglionic section of the sympathetic fibers in the dog.

SUMMARY

Experiments on dogs were performed to study the effects of lumbar sympathectomy on the peripheral circulation of the hind limbs. Significant rises of distal cutaneous temperatures and arterial blood flow and a decrease of peripheral arterial pressure followed preganglionic denervation. Epinephrine was injected intravenously immediately after unilateral sympathectomy. An increase of peripheral arterial blood pressure and flow, of greater extent and duration than on the control side, was noted. Because of the disagreement that exists as to the time of onset of sensitization to epinephrine, further experiments were performed on dogs after unilateral lumbar sympathectomy. When the continuity of the femoral arteries was maintained, no difference in the effect of epinephrine on the peripheral arterial pressures of the limbs could be demonstrated, but a difference was very evident when the peripheral arterial beds were isolated.

In control animals, administration of epinephrine resulted in a brief rise of pressure and outflow in the femoral veins, coincident with the first part of the rise of arterial pressure. The pressures and flow then abruptly decreased to the control level, or less, during the latter portion of the arterial response. This also occurred after sympathectomy, but was less marked on the denervated side.

Finally, plethysmographic studies were carried out on an intact and on a denervated kidney. Epinephrine given immediately after the postganglionic denervation similarly resulted in a greater decrease of volume and a longer duration of the effect in the denervated organ. These data suggest strongly that hypersensitivity of blood vessels to epinephrine may occur *immediately* after both preganglionic and postganglionic sympathectomy.

REFERENCES

1. Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Arteriovenous Fistula: Experimental Study of Influence of Sympathetic Nervous System on Development of Collateral Circulation, *Surg., Gynec. & Obst.* 84:629, 1947.
2. Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Experimental Studies of Arteriovenous Fistula With Regard to the Development of Collateral Circulation, *Proc. Staff Meet., Mayo Clin.* 22:495, 1947.
3. Eckstein, R. W., Gregg, D. E., and Pritchard, W. H.: The Magnitude and Time of Development of the Collateral Circulation in Occluded Femoral, Carotid, and Coronary Arteries, *Am. J. Physiol.* 132:351, 1941.
4. Sheard, Charles: Skin Temperatures and Thermal Regulation of the Body, With Special Reference to the Extremities: Measurement and Significance Under Various Physical and Physiological Conditions. In: Glasser, Otto: *Medical Physics*, Chicago, 1944, The Year Book Publishers, Inc., p. 1523.
5. Theis, F. V.: Effect of Sympathetic Neurectomy on the Collateral Arteriolar Circulation of the Extremities, *Surg., Gynec. & Obst.* 57:737, 1933.
6. Smithwick, R. H.: Surgical Treatment of Hypertension: The Effect of Radical (Lumbosacral) Splanchnicectomy on the Hypersensitive State of One Hundred Fifty-Six Patients Followed One to Five Years, *Arch. Surg.* 49:180, 1944.
7. Leriche, René, and Fontaine, René: Mise en évidence par l'expérimentation d'un système de régulation vasomotrice périphérique indépendant de la régulation circulatoire générale, *Arch. d. mal du coeur* 21:778, 1928.
8. Frieh, P., and Nassi, J.: Quelques faits expérimentaux au sujet de la scurocainisation de la chaîne lombaire comparée à ceux de la section. Effets sur la tension périphérique, *Rev. de chir., Paris* 74:231, 1936.
9. Meltzer, S. J., and Meltzer, Clara: The Share of the Central Vasomotor Innervation in the Vasoconstriction Caused by the Intravenous Injection of Suprarenal Extract, *Am. J. Physiol.* 9:147, 1903.
10. Elliott, T. R.: The Action of Adrenalin, *J. Physiol.* 32:401, 1905.
11. Freeman, N. E., Smithwick, R. H., and White, J. C.: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting From Insulin Hypoglycemia, *Am. J. Physiol.* 107:529, 1934.
12. Smithwick, R. H., Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity; An Additional Cause of Failure of Operations for Raynaud's Disease, *Arch. Surg.* 29:759, 1934.
13. Meltzer, S. J., and Auer, Clara M.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin. I. The Effect of Subcutaneous Injections and Instillations of Adrenalin Upon the Pupils of Rabbits, *Am. J. Physiol.* 11:28, 1904.
14. Meltzer, S. J.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin. II. On the Influence of Subcutaneous Injections of Adrenalin Upon the Eyes of Cats After Removal of the Superior Cervical Ganglion, *Am. J. Physiol.* 11:37, 1904.
15. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamine and of Some Other Substances, *J. Physiol.* 52:110, 1918.
16. Rosenbleuth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Organs. XXVIII. Some Effects of Sympathin on the Nictitating Membrane, *Am. J. Physiol.* 99:398, 1932.
17. Daniélopou, D., Aslan, A., and Marcou, I.: Quoted by Fatherree, Adson, and Allen.²³
18. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, With Special Reference to the Effects of Denervation, *Clin. Sc.* 2:1, 1935.
19. Hampel, C. W.: The Effect of Denervation on the Sensitivity of Adrenaline of the Smooth Muscle in the Nictitating Membrane, of the Cat, *Am. J. Physiol.* 111:611, 1935.
20. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Vasomotor Tonus of the Denervated Artery. Control of Sympathectomized Blood Vessels by Sympathomimetic Hormones and Its Relation to the Surgical Treatment of Patients With Raynaud's Disease, *Arch. Neurol. & Psychiat.* 36:1251, 1936.
21. Ascroft, P. B.: The Basis of Treatment of Vasoospastic States of the Extremities: An Experimental Analysis on Monkeys, *Brit. J. Surg.* 24:787, 1937.
22. Fatherree, T. J., and Allen, E. V.: The Influence of Epinephrine on the Digital Arterioles of Man: A Study of the Vasoconstrictor Effects, *J. Clin. Investigation* 17:109, 1938.
23. Fatherree, T. J., Adson, A. W., and Allen, E. V.: The Vasoconstrictor Action of Epinephrine on the Digital Arterioles Before and After Sympathectomy, *Surgery* 7:75, 1940.
24. Grimson, K. S.: Sympathectomy and the Circulation—Anatomic and Physiologic Considerations and Early and Late Limitations, *Surgery* 19:277, 1946.

DIFFERENTIATION OF THE CHANGES IN THE Q-T INTERVAL IN HYPOCALCEMIA AND HYPOPOTASSEMIA

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IT HAS been known for some time that both hypocalcemia^{1,2,3} and hypopotassemia^{3,4} may cause prolongation of the Q-T interval of the electrocardiogram. Little attention has been directed to the fact, however, that the electrocardiographic patterns of the two conditions can be differentiated on the basis of the length of the RS-T segments and the configuration of the T waves. In the present communication the distinguishing features of the electrocardiogram in hypopotassemia will be described and contrasted with the findings in hypocalcemia.

MATERIAL AND RESULTS

CASE 1. *Hypocalcemia Due to Idiopathic Hypoparathyroidism.*—A white, single, unemployed man, 24 years of age, was admitted to the Clinic on April 27, 1942, because of failing vision, occasional numbness, stiffness, and cramping of the hands, and inconstant difficulty in swallowing. All of the symptoms were of approximately two years' duration. The only abnormal findings on physical examination consisted of mature cataracts in both eyes, a positive Trousseau's sign, and unusual changes in the fingernails, consisting of a depression at the base of each nail. The urinalysis and blood count gave normal results, and the Wassermann reaction of the blood was negative. The serum calcium content was 4.4 mg. per 100 c.c. on the day of admission and the serum phosphorus was 5.9 milligrams. These measurements were repeated on May 2 with almost identical results.

An electrocardiogram was made on April 29 and showed changes characteristic of hypocalcemia (Fig. 1). Sinus rhythm was present with a rate of 70 per minute, and the only abnormality consisted of prolongation of the Q-T interval to 0.60 second (Table I). Correction of this value according to Bazett's formula⁵ gave a constant of 0.65 (upper limit of normal for men, 0.392). The lengthening of the Q-T interval was due entirely to prolongation of the RS-T segments, which measured 0.32 second in duration, as compared with an upper limit of normal of 0.135 second in men at a heart rate of 70 per minute.⁶

CASE 2. *Hypopotassemia During and After Treatment of Diabetic Coma.*—A Negro laborer, 42 years of age, was admitted to the hospital on Oct. 9, 1946, in diabetic coma of a few hours' duration. Physical examination revealed no abnormal cardiac findings. The urine contained 4 plus sugar and 4 plus acetone, and the blood sugar content was 516 mg. per 100 cubic centimeters. The carbon dioxide combining power of the plasma was 11.8 volumes per 100 c.c. and the serum potassium content was 8.6 mg. per 100 cubic centimeters. Treatment consisted of large doses of insulin, intravenous administration of Ringer's solution, and a 500 c.c. transfusion of whole blood. The clinical response was satisfactory.

From the Cleveland Clinic.

Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

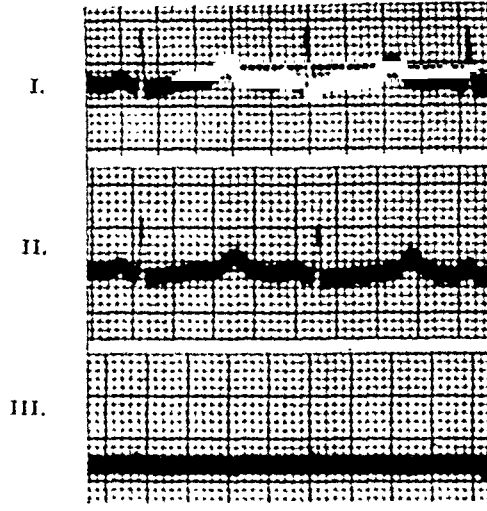


Fig. 1.—Case 1. Electrocardiogram in hypocalcemia.

An electrocardiogram taken shortly after the patient's admission showed sinus tachycardia with a rate of 102 per minute (Fig. 2). The P-R intervals and QRS complexes were of normal normal duration (Table I). The RS-T segments were of normal length but were slightly depressed in Leads II, III, and CF₄. Low, rounded T waves were present in Lead I, but the length of the Q-T interval could not be measured accurately because the descending limb of the T

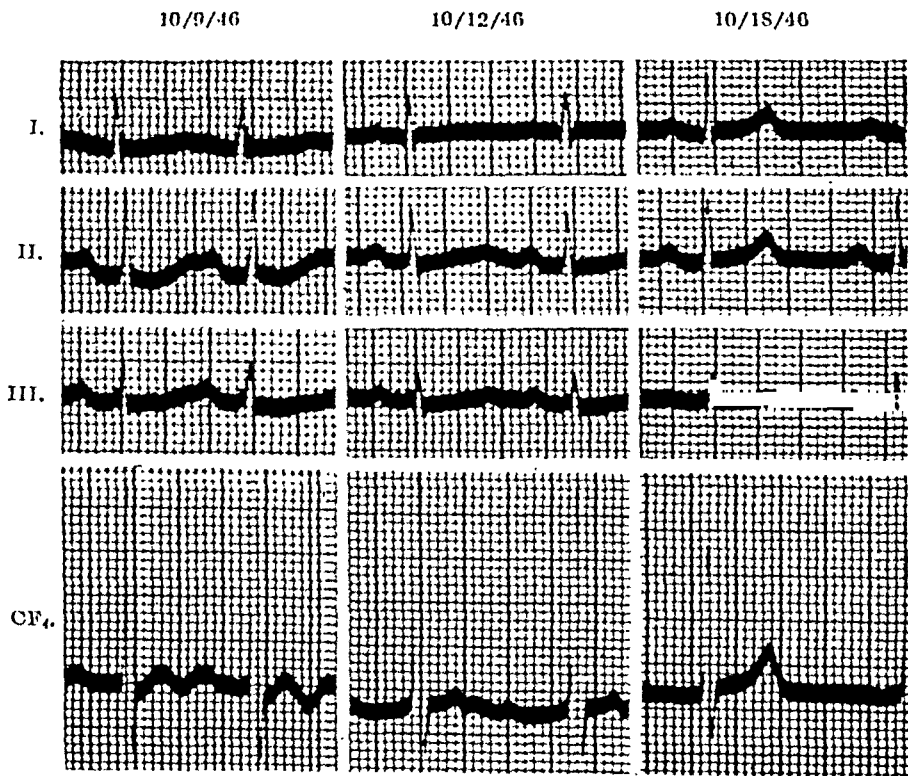


Fig. 2.—Case 2. Hypokalemia during and after treatment of diabetic coma. The serum potassium content was 8.6 mg. per 100 c.c. on October 9, 10.5 mg. on October 12, and 21.1 mg. on October 18.

TABLE I. SUMMARY OF OBSERVATIONS

CASE NO.	SEX	DATE	ELECTROCARDIOGRAPHIC FINDINGS						SERUM CHEMISTRY		
			HEART RATE	DURATION IN SECONDS							
				P-R	QRS	RS-T	T	Q-T	Q-Tc*	K (MG. PER 100 C.C.)	Ca (MG. PER 100 C.C.)
1	M	4/27/42 4/29/42 5/ 2/42	70	0.12	0.08	0.32	0.20	0.60	0.65		4.4
2	M	10/ 9/46 10/12/46	102 83	0.20 0.20	0.06 0.07	0.11 0.10	0.29 0.31	0.46 0.48	0.60 0.57	8.6 10.5	4.5
		10/18/46	65	0.20	0.07	0.10	0.22	0.39	0.41	21.1	9.0
3	F	6/11/42 6/18/42	98 103	0.16 0.15	0.06 0.06	0.13 0.11	0.19 0.14	0.38 0.31	0.48 0.40	7.0	9.0
		6/19/42								16.0	8.7
4	M	3/ 1/43 3/ 3/43	76 87	0.18 0.16	0.11 0.09	0.05 0.06	0.20 0.20	0.36 0.35	0.41 0.42	7.0 14.0	9.6
5	F	4/ 5/40 5/ 1/40	49	0.20	0.08	0.14	0.28	0.50	0.45	5.4 16.1	7.9 9.8
6	F	5/ 2/47 11/ 6/46	66 76	0.21 0.20	0.08 0.11	0.12 0.09	0.22 0.37	0.42 0.57	0.44 0.64		11.2
		11/12/46	91	0.17	0.10	0.08	0.32	0.50	0.62	3.9 10.1	
		11/15/46 11/16/46 11/17/46	83	0.16	0.08	0.06	0.20	0.34	0.40	25.4	10.3

Q-T interval in seconds

*Calculated according to Bazett's formula: $Q-T \text{ corrected} =$

$\frac{Q-T \text{ interval in seconds}}{\sqrt{\text{Cardiac cycle in seconds}}}$

The upper limit of normal for men is 0.392 and for women 0.44.⁵

wave was deformed near its termination by a small P wave. The duration of the interval appeared to be at least 0.46 second, however, and correction of this value according to Bazett's formula gave a constant of 0.60. In Leads II and III the T waves were distorted shortly after reaching their maximum amplitude by a wave which was either a P wave or a combined U wave and P wave. Unusually prominent U waves were present in Lead CF₄, but no P waves could be identified.

On the third day after admission the serum potassium concentration was 10.5 mg. per 100 c.c., and the serum calcium was 9.0 milligrams. An electrocardiogram (Fig. 2) showed sinus rhythm with a rate of 83 per minute. The depression of the RS-T segments had disappeared. The T waves were almost flat in Lead I, but, nevertheless, were obviously much broader than normal. In Leads II and III, the T waves were low, broad, and rounded, and the duration of the Q-T interval was 0.48 second. Correction of this value according to Bazett's formula gave a constant of 0.57. No U waves could be identified in the limb leads, but in Lead CF₄ a prominent U wave was present.

On October 16 and 17 the patient was given potassium nitrate by mouth in doses of 2.0 Gm. four times daily. The serum potassium content on October 18 was 21.1 mg. per 100 cubic centimeters. An electrocardiogram made on this day (Fig. 2) showed sinus rhythm with a rate of 65 per minute. The Q-T intervals were much shorter than formerly, and correction according to Bazett's formula now gave a constant of 0.41, only slightly above normal. The T waves were sharply peaked, much narrower, and of greater amplitude in Leads I and II, but were still low in Lead III. There were no U waves in the limb leads or in Lead CF₄.

Comment: The electrocardiograms in this case illustrate the changes which result from a great reduction in the potassium content of the blood serum and demonstrate that the abnormalities are corrected by restoration of the potassium concentration to normal. The most striking changes during hypopotassemia consisted of alterations in the T waves and lengthening of the Q-T interval. In the limb leads the T waves were low, rounded, and prolonged, and it was their increased duration which was entirely responsible for the lengthening of the Q-T interval. In contrast to the electrocardiographic findings in hypocalcemia, the RS-T segments were of normal length.

When the serum potassium was at its lowest level, the RS-T segments were slightly depressed in Leads I and II, and the T waves in all three limb leads were deformed by a wave which was either a P wave or a combined U wave and P wave. An unusually prominent U wave was present in Lead CF₄. In the second record, made after the potassium concentration had risen slightly, the T waves were of smooth contour in the limb leads, and no U waves could be distinguished. A prominent U wave was still present in Lead CF₄, however, and its position suggested that a U wave might be completely fused with the T waves in the limb leads. If fusion of this kind were actually present, it could well account for at least a part of the increased duration of the T waves.

When the serum potassium content had been restored to normal, the T waves became taller, peaked, and of normal width, and the duration of the Q-T interval, corrected for the heart rate, diminished to a value only slightly above the upper limit of normal. No U waves could be distinguished in the limb leads or in Lead CF₄.

CASE 3. Hypopotassemia Following Diabetic Acidosis.—A white, married woman, 31 years of age, was admitted to the hospital on June 9, 1942, because of drowsiness of several hours' duration. Physical examination revealed no abnormal cardiac findings. The urine had a specific gravity of 1.029, contained a trace of albumin, and gave a 4 plus reaction for sugar and acetone. The blood sugar content was 370 mg. per 100 c.c., and the carbon dioxide combining power of the plasma was 9 volumes per 100 cubic centimeters.

During the first two days of treatment, the patient received 445 units of insulin, 1,000 c.c. of a 10 per cent glucose solution in physiologic saline solution by intravenous injection, 3,000 c.c. of a 3 per cent glucose solution by hypodermoclysis, and 500 c.c. of a 5 per cent sodium bicarbonate solution intravenously. On the morning of the third day, the fasting blood sugar content was 272-mg. per 100 c.c. and the carbon dioxide combining power of the plasma was

53.8 volumes per 100 cubic centimeters. The serum potassium content was 7.0 mg. per 100 c.c. and the serum calcium was 9.0 milligrams. An electrocardiogram made on this day (Fig. 3) showed sinus rhythm with a rate of 98 per minute. The P-R intervals, QRS complexes, and RS-T segments were of normal duration (Table I). The Q-T interval measured 0.38 second, and correction according to Bazett's formula gave a constant of 0.48. The upper limit of normal for this value in women is 0.44.⁵ The T waves were broad, low, and moderately rounded in Leads I and II and were diphasic and low in Lead III. A small U wave could be distinguished inconstantly in Lead II.

6/11/42

6/18/42

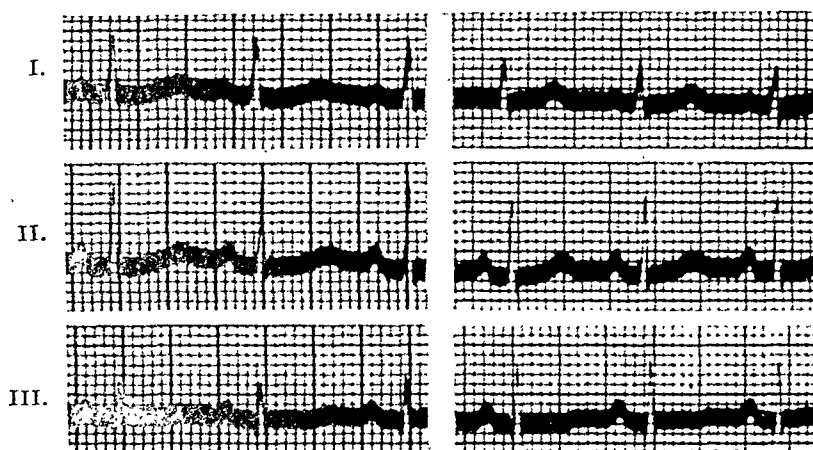


Fig. 3.—Case 3. Hypokalemia following diabetic acidosis. The serum potassium content was 7.0 mg. per 100 c.c. on June 11 and 16.0 mg. on June 19.

The subsequent clinical course was uneventful, and the blood sugar content was satisfactorily regulated by diet and insulin. An electrocardiogram made one week after the first record (Fig. 3) showed sinus tachycardia with a rate of 103 per minute. The T waves, although of approximately the same amplitude as formerly, were sharper and narrower. The duration of the Q-T interval was 0.31 second, and correction according to Bazett's formula gave a constant of 0.40, a normal value. On the morning after this record was made the serum potassium content was 16.0 mg. per 100 c.c. and the serum calcium was 8.7 milligrams.

Comment: Hypokalemia in this patient, as in Case 2, caused prolongation of the Q-T interval due entirely to increased duration of the T waves. The length of the RS-T segments was not affected. The T waves were low and rounded in Leads I and II of the tracing made while the serum potassium content was low. Although the return of the potassium content to normal did not appreciably affect the amplitude of these waves, the waves did become narrower and peaked, and there was a simultaneous return of the Q-T interval to normal length. Unlike the findings in the preceding case, hypokalemia in this instance did not cause the appearance of prominent U waves.

CASE 4. Hypokalemia Following Diabetic Acidosis.—A white male student, 20 years of age, was admitted to the hospital on Feb. 26, 1943, in a semistuporous condition. Physical examination revealed no abnormal cardiac findings. The urine had a specific gravity of 1.025 and contained 1 plus albumin, 4 plus sugar, and 4 plus acetone. The blood sugar content was 560 mg. per 100 c.c. and the carbon dioxide combining power of the plasma was 11.8 volumes per 100 cubic centimeters.

Treatment consisted of large doses of insulin and the intravenous administration of 1,000 c.c. of a 10 per cent glucose solution in physiologic saline and 500 c.c. of a 5 per cent sodium bicarbonate solution. On the morning after admission the fasting blood sugar content was 116 mg. per 100 c.c., the carbon dioxide combining power of the plasma was 39.5 volumes per 100

c.c., the serum potassium concentration was 6.6 mg. per 100 c.c., and the serum calcium was 10.1 milligrams. The blood sugar content subsequently remained well controlled.

An electrocardiogram was made on March 1 and showed sinus rhythm with a rate of 76 per minute (Fig. 4). The P-R intervals were of normal length, but the QRS complexes were prolonged to 0.11 second (Table I). The Q-T intervals were slightly longer than normal and the T waves were low and rounded in all leads. U waves were present in Leads II and III (although they could be distinguished only with difficulty) and by partial fusion with the descending limb of the T waves gave the superficial appearance of considerably prolonged Q-T intervals. The serum potassium content on the morning the record was made was 7.0 mg. per 100 c.c. and the serum calcium was 9.6 milligrams.

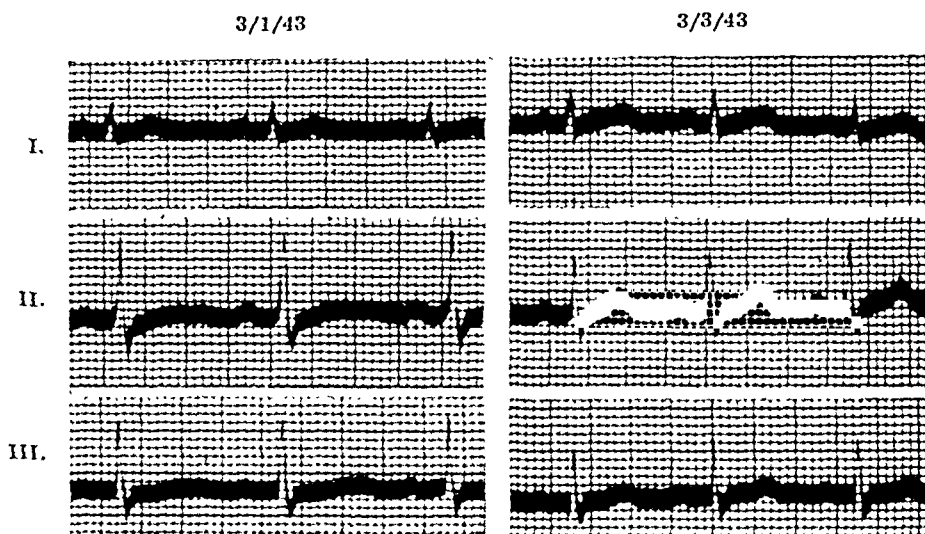


Fig. 4.—Case 4. Hypopotassemia following diabetic acidosis. The serum potassium content was 7.0 mg. per 100 c. c. on March 1 and 14.0 mg. on March 3.

The patient received 8.0 Gm. of potassium nitrate in divided doses by mouth on March 2. On March 3 the serum potassium content was 14.0 mg. per 100 c.c. and the serum calcium 9.6 milligrams. An electrocardiogram showed sinus rhythm with a rate of 87 per minute. The P-R intervals and QRS complexes were of normal duration. The length of the Q-T intervals was essentially the same as in the earlier record, but the T waves were of greater amplitude and peaked in all leads, and the U waves had disappeared.

Comment: In this case the duration of the Q-T interval and the width of the T waves were not affected by a rise in the serum potassium content from 7.0 mg. to 14.0 mg. per 100 cubic centimeters. When the serum potassium concentration was at the lower level, however, the T waves were low and rounded, and the duration of the QRS complexes was slightly increased. U waves were present in Leads II and III and by partial fusion with the descending limb of the T waves resulted in what at first glance appeared to be a prolonged Q-T interval. When the serum potassium content rose to 14.0 mg. per 100 c.c., the T waves increased in amplitude and became sharper, the duration of the QRS complexes returned to normal, and the U waves disappeared. The duration of the Q-T interval was still slightly greater than normal, and it is possible that a further rise in the serum potassium concentration might have resulted in narrowing of the T waves and a consequent return of the length of Q-T to normal.

CASE 5. Hypopotassemia Due to Overtreatment With Desoxycorticosterone Acetate.—A white widow, 40 years of age, who had been under treatment for Addison's disease for three years, received subcutaneous implants of desoxycorticosterone acetate on Oct. 3, 1939, and Jan. 5, 1940, in amounts of 198.0 mg. and 256.0 mg., respectively. Additional measures of treatment

after the first implant consisted of a diet low in potassium content with 20.0 Gm. of sodium chloride added daily, aqueous adrenal cortical extract in amounts ranging from 1.0 to 10 c.c. daily, and desoxycorticosterone acetate in doses varying from 5.0 mg. every other day to 10.0 mg. daily. On March 5, 1940, because of persistent and increasing weakness, drowsiness, headache, occasional periods of confusion, and intermittent pain in the abdomen, the pellets of desoxycorticosterone acetate were removed. The potassium content of the blood serum on the preceding day had been 5.7 mg. per 100 cubic centimeters. The diet and supplementary sodium chloride were continued as before, and the patient also continued to receive desoxycorticosterone acetate in doses of 5.0 or 10.0 mg. daily. There was considerable improvement, but occasional periods of weakness, muscular pain, abdominal distress, and edema about the eyes continued to occur.

An electrocardiogram on April 5, 1940 (Fig. 5), showed sinus bradycardia with a rate of 49 per minute. The P-R intervals and QRS complexes were of normal duration (Table I). The RS-T segments were of normal length, but were slightly depressed in Leads I and II and slightly elevated in Lead III. The striking feature of the record consisted of low, rounded T waves of increased duration in all limb leads. The Q-T interval measured 0.50 second and correction according to Bazett's formula gave a constant of 0.45. In Leads II and III the T waves merged with a U wave before returning to the isoelectric level, and this gave the appearance of considerable lengthening of the Q-T interval in these leads.

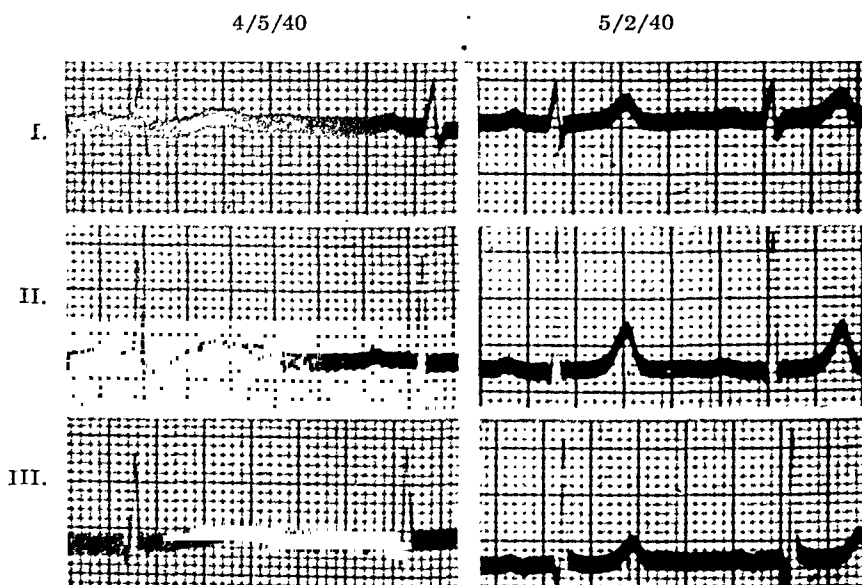


Fig. 5.—Case 5. Hypopotassemia due to overtreatment with desoxycorticosterone acetate. The serum potassium content was 5.4 mg. per 100 c. c. on April 5 and 16.1 mg. on May 1.

Physical examination on the day of this record revealed a poorly nourished, rather apathetic individual. The temperature was 98° F., and the blood pressure was 108/70. There was slight edema about the eyes. The heart and lungs were normal on percussion and auscultation. There was no peripheral edema. Urinalysis gave normal findings except for a faint trace of albumin and 10 to 12 pus cells per high power field in the sediment. The red blood cell count was 3,940,000 and the hemoglobin content 71 per cent. The white blood cell count was 5,850. The serum potassium content was 5.4 mg. per 100 c.c. and the serum calcium 7.9 milligrams.

The administration of desoxycorticosterone acetate was discontinued on April 9. On May 1 the serum potassium content was 16.1 mg. per 100 c.c. and the serum calcium 9.8 milligrams. An electrocardiogram (Fig. 5) on the following day showed sinus rhythm with a rate of 66 per minute. The P-R interval measured 0.21 second but the QRS complexes, RS-T segments, and

Q-T intervals were of normal duration. The record was strikingly different from the earlier tracing, however, in that the T waves were of greater amplitude, decidedly narrower, and peaked in all leads. The prominent U waves formerly present were not longer discernible.

Comment: In this case the Q-T interval was not significantly prolonged during hypopotassemia, and the duration of the corrected interval remained essentially unchanged after the potassium content of the serum had returned to normal. During hypopotassemia, however, the T waves were low, rounded, and of increased duration in all leads, and in Leads II and III they merged with a U wave before returning to the isoelectric level. This fusion of T waves and U waves gave the appearance of considerable lengthening of the Q-T interval in the latter leads. After the serum potassium content had returned to normal, the T waves were of greater amplitude, peaked, and decidedly narrower in all leads and the formerly prominent U waves were no longer present.

The findings in this case, when considered in conjunction with those in the preceding cases, indicate that the earliest electrocardiographic change in hypopotassemia consists of rounding, widening, and usually diminution in amplitude of the T waves. Whether or not the Q-T interval becomes prolonged is determined solely by the degree to which the duration of the T waves is increased.

The first electrocardiogram in this case was made at a time when the serum calcium content was 7.9 mg. per 100 c.c., but the absence of significant lengthening of the RS-T segment and Q-T interval indicates that the hypocalcemia had no effect upon the record.

CASE 6. Hypopotassemia of Uncertain Cause.—A white, single girl, 18 years of age, was admitted to the hospital on Nov. 5, 1946, because of persistent but variable edema of the face, hands, abdominal wall, and lower extremities, two years in duration. The illness apparently had begun shortly after she had broken her engagement to be married, and a brother had been severely burned in an accident. An accurate dietary history could not be obtained, but the appetite had been poor and the food intake definitely restricted. Occasionally there was vomiting after a meal. In an effort to control the edema, laxatives had been taken each night since the onset of the illness, and these had produced a chronic, watery diarrhea. The menses had been normal until a period of amenorrhea which lasted from July, 1945, until May, 1946, and following this they were irregular in regard to interval and duration. For three months before her admission the patient had received daily injections of a mercurial diuretic. There had been rapid fluctuations in the body weight, and at different times she had weighed as little as 90 pounds and as much as 134 pounds.

Physical examination revealed a small, poorly nourished girl with scanty axillary and pubic hair, dry skin, and brittle nails. The temperature was 97.8° F., the pulse rate 92, and the blood pressure 90/40. The pupils reacted normally, and ophthalmoscopic examination showed no diagnostic changes. The lungs were clear and the heart normal except for a moderate systolic murmur at the apex. The deep reflexes were sluggish in the arms and could not be obtained in the lower extremities. There was slight pitting edema of the legs.

The urine contained a trace of albumin, an occasional hyaline or finely granular cast, and a rare red blood cell. The blood count was normal. The blood urea content was 100 mg. per 100 c.c., the serum calcium 11.2 mg., and the serum phosphorus 4.3 milligrams. The total serum protein content was 6.2 grams per 100 c.c. and the Wassermann reaction of the blood was negative.

An electrocardiogram was made on the day after admission and showed sinus rhythm with a rate of 76 per minute (Fig. 6). The P-R intervals were of normal length, but the QRS complexes were prolonged to 0.11 second (Table I). The RS-T segments were of normal duration but were slightly depressed in all leads. The Q-T interval was prolonged to 0.57 second and correction according to Bazett's formula gave a constant of 0.64. The T waves were low in Lead I and large, rounded, and broad in Leads II and III. No U waves were apparent in the limb leads, but in Lead CF₄ the T waves had two peaks and the second of these appeared to be a U wave. It seemed probable, therefore, that the increased broadness of the T waves in the limb leads was due in part to fusion with a U wave.

Because of the electrocardiographic findings the serum potassium was measured on November 12, and another electrocardiogram was made. The serum potassium content was 3.9 mg. per 100 cubic centimeters. The electrocardiogram (Fig. 6) showed sinus rhythm with a rate of 91 per minute. The P-R interval and QRS complexes were of normal duration. The RS-T segments were of normal length but were depressed in Leads I, II, and CF₄. The Q-T interval was prolonged to 0.50 second and correction according to Bazett's formula gave a constant of 0.62. The T waves were broad in all leads, low in Lead I, and prominent and rounded in Leads II and III. No U waves could be distinguished in the limb leads, but a probable U wave was present in Lead CF₄.

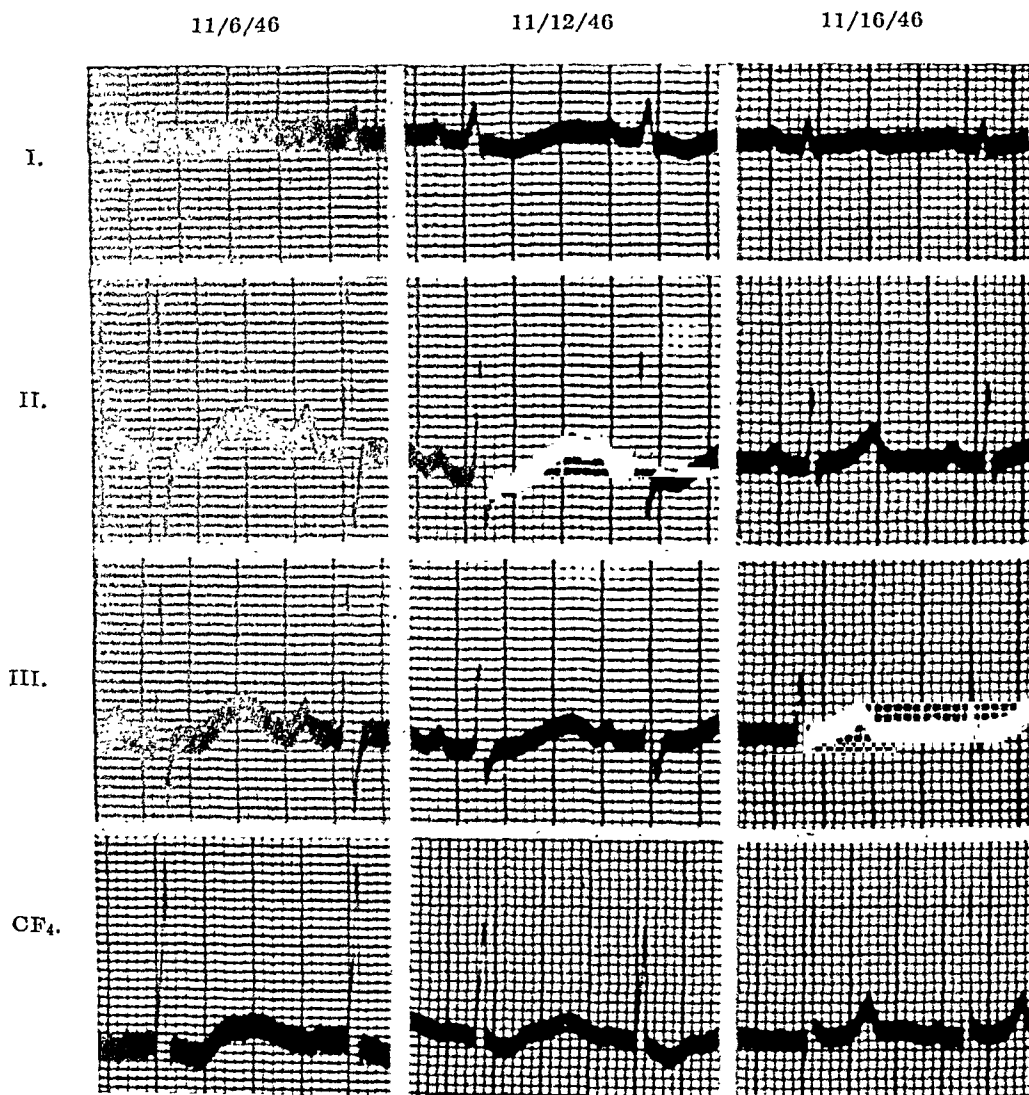


Fig. 6.—Case 6. Hypokassemia of uncertain cause. The serum potassium content was 3.9 mg. per 100 c.c. on November 12, 10.1 mg. on November 15, and 25.4 mg. on November 17.

On November 13 the patient received 15.0 Gm. of potassium nitrate by mouth, and on November 15, 30.0 Gm. of potassium chloride. The serum potassium content on November 15 was 10.1 mg. per 100 c.c. and on November 17, 25.4 mg. per 100 cubic centimeters. An electrocardiogram on November 16 (Fig. 6) showed sinus rhythm with a rate of 83 per minute. The P-R intervals, QRS complexes, and Q-T intervals were of normal duration. The RS-T segments were no longer depressed in Leads I and II, and the T waves were strikingly different

from those in the earlier records, being of greater amplitude in Lead I, sharply peaked in Leads II, III, and CF₄, and of shorter duration in all leads. No U waves were present in any lead.

Comment: Hypopotassemia in this case caused slight but inconstant prolongation of the QRS complexes, depression of the RS-T segments, and lengthening of the Q-T intervals by unusually broad T waves. In Leads II and III, the T waves were of considerably greater amplitude than in the preceding cases. Comparison of the limb leads with Lead CF₄ suggested that the increased duration of the T waves in the former leads was due in part to fusion of the T waves with U waves. That all of the changes were related causally to the low serum potassium content was demonstrated by their prompt disappearance when the hypopotassemia was corrected by the oral administration of potassium salts.

REVIEW OF THE LITERATURE

There are but few earlier reports concerning the effect of hypopotassemia on the electrocardiogram of man. The first observations were made by Stewart, Smith, and Milhorat⁴ in a study of a patient with familial periodic paralysis. In addition to prolongation of the Q-T interval and changes in the form of the T wave similar to those recorded in the present investigation, there was increased duration of the P-R interval and QRS complexes and alteration of the form of the RS-T segments. Attention was directed to the fact that the lengthening of the Q-T interval differed from the lengthening observed in hypocalcemia, inasmuch as the change in the latter condition is due to increased duration of the isoelectric RS-T segment. This is the only earlier report in which the difference between the electrocardiogram of hypopotassemia and that of hypocalcemia is pointed out.

Electrocardiographic studies in a case of periodic paralysis also were made by Stoll and Nisnewitz.⁷ During a moderately severe attack, at which time the serum potassium content was 11.0 mg. per 100 c.c., the P-R interval was 0.28 second and the T waves were flat in Lead I and low, rounded, and broad in Leads II and III. The Q-T interval and duration of the QRS complexes were not measured, but both appear to be slightly prolonged in the published records. The changes disappeared after recovery from the paralysis, and this was found to be true whether the termination of an attack was spontaneous or was induced by the administration of potassium.

Holler⁸ described the electrocardiographic changes observed in a case of diabetic acidosis with hypopotassemia. At a time when the serum potassium content was 9.8 mg. per 100 c.c., the electrocardiogram showed depression of the RS-T segments and low T waves in the limb leads. The duration of the Q-T interval cannot be measured in the published tracing because the descending limb of the T wave is interrupted by a P wave. The abnormalities disappeared when the serum potassium concentration was restored to normal.

It is well known that overtreatment of Addison's disease with desoxycorticosterone acetate results in a decrease in the serum potassium content, and a few reports are available in which electrocardiograms have been made during treatment with the drug. Thomson⁹ published a series of records which show widening and diminution in amplitude of the T waves and prolongation of the Q-T interval as the serum potassium concentration fell from 31.6 mg. per 100 c.c. to 8.3 milligrams. Currens and White¹⁰ observed flat or slightly inverted

T waves in all the limb leads of two patients with Addison's disease who had developed evidence of congestive heart failure while under treatment with desoxycorticosterone acetate. The Q-T interval was not prolonged in either patient, and there were no measurements of the serum potassium at the time the electrocardiograms were made.

Brown, Currens, and Marchand¹¹ described the electrocardiographic abnormalities recorded in two patients with muscular paralysis due to chronic nephritis, and attributed the changes to potassium loss. In the first case, partial auriculoventricular block was present, the RS-T segments were depressed, and the T waves were low and broad in all leads. Measurements of the serum potassium content were not made, but the electrocardiogram was normal on the day after administration of potassium chloride. In the second case, the T waves were low in all leads, the RS-T segments were slightly depressed, and a prominent U wave was present in Lead IV F. The serum potassium was not measured during the period of muscular weakness, and potassium salts were not administered.

Rapoport and his associates¹² observed lowered T waves in infants suffering from diarrhea and demonstrated that these changes were corrected by the administration of potassium salts. No electrocardiograms were published.

Ellis¹³ recently reported a study of the electrocardiograms of four prisoners of war suffering from severe malnutrition and diarrhea. The published records show changes remarkably similar to those observed in the present investigation, and it seems highly probable, therefore, that the abnormalities were due principally to diminished serum potassium concentration. The most striking and constant changes consisted of prolongation of the Q-T interval, broad, abnormal T waves, and large U waves. Inspection of the tracings shows that the lengthening of the Q-T interval was due to the increased duration of the T waves. In two cases the P-R interval was slightly and inconstantly increased, and in one the duration of the QRS complexes was prolonged. Treatment of the patients with corrective diets and added vitamins resulted in return of the records to normal.

DISCUSSION

The results of the present investigation confirm and extend the earlier observations concerning the effect of hypopotassemia on the electrocardiogram and illustrate the manner in which the changes due to hypopotassemia differ from those associated with hypocalcemia. They demonstrate that the earliest effect of a low serum potassium content consists of rounding and broadening of the T waves. The T waves generally decrease in amplitude also, but this is not always the case. The Q-T interval is frequently prolonged, and whether or not this change occurs is determined entirely by the degree to which the duration of the T waves is increased. The RS-T segments are not lengthened but are often slightly depressed. The duration of the QRS complexes is increased occasionally. Prominent U waves commonly appear in the limb leads and Lead CF_1 and, by partial fusion with the descending limb of the T waves, may cause

further apparent lengthening of the Q-T interval. Although the presence of U waves has been noted in some of the earlier reports, the frequency of their occurrence has not been emphasized heretofore.

It was not possible in the present study to establish a critical level of serum potassium concentration at which the electrocardiographic changes of hypopotassemia appear.

In contrast to the findings in hypopotassemia, the electrocardiographic pattern in hypocalcemia is of a simple nature and consists entirely of prolongation of the Q-T interval due to lengthening of the RS-T segment. The duration of the P-R intervals and QRS complexes is not increased, the RS-T segments remain isoelectric, and the T waves are not altered in contour, amplitude, or duration. Prominent U waves do not occur.

The electrocardiographic findings in hypopotassemia and hypocalcemia are of clinical importance, for their recognition may suggest the presence of a condition that otherwise might not be suspected.

SUMMARY

1. The electrocardiographic findings have been described in a typical case of hypocalcemia and in five cases of hypopotassemia due to various causes.

2. Hypopotassemia is characteristically attended by rounded T waves of increased duration and usually of low amplitude. When the widening of the T waves attains a sufficient degree, prolongation of the Q-T interval results. The RS-T segments are not lengthened but often are slightly depressed. Prominent U waves are commonly present and by partial fusion with the descending limb of the T waves may cause further apparent lengthening of the Q-T interval. The duration of the QRS complexes is occasionally increased.

3. In contrast to the findings in hypopotassemia, the electrocardiographic pattern of hypocalcemia is of a simple nature and consists entirely of prolongation of the Q-T interval due to lengthening of the RS-T segment.

REFERENCES

1. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7:387, 1929.
- ✓ 2. Barker, P. S., Johnston, F. D., and Wilson, F. N.: The Duration of Systole in Hypocalcemia, *AM. HEART J.* 14:82, 1937.
3. Wofford, C. P., and Ernstene, A. C.: The Diagnostic Significance of an Increased Q-T Interval in the Electrocardiogram, *Cleveland Clin. Quart.* 8:12, 1941.
4. Stewart, H. J., Smith, J. J., and Milhorat, A. T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, *Am. J. M. Sc.* 199:789, 1940.
5. Bazett, H. C.: An Analysis of the Time-Relations of Electrocardiograms, *Heart* 7:353, 1920.
6. Ashman, R., and Hull, E.: *Essentials of Electrocardiography for the Student and Practitioner of Medicine*, ed. 2, New York, 1941, The Macmillan Company.
7. Stoll, B., and Nisnewitz, S.: Electrocardiographic Studies in a Case of Periodic Paralysis, *Arch. Int. Med.* 67:755, 1941.

8. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **131**:1186, 1946.
9. Thomson, W. A. R.: Potassium and the T wave of the Electrocardiogram, Lancet **1**:808, 1939.
10. Currens, J. H., and White, P. D.: Congestive Heart Failure and Electrocardiographic Abnormalities Resulting From Excessive Desoxycorticosterone Acetate Therapy in the Treatment of Addison's Disease, AM. HEART J. **28**:611, 1944.
11. Brown, M. R., Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting From Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545, 1944.
12. Rapoport, S., Dodd, K., Clark, M., and Syllm, I.: Postacidotic State of Infantile Diarrhea; Symptoms and Chemical Data, Am. J. Dis. Child. **73**:391, 1947.
13. Ellis, L. B.: Electrocardiographic Abnormalities in Severe Malnutrition, Brit. Heart J. **8**:53, 1946.

THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY AS OBTAINED BY UNIPOLAR PRECORDIAL AND LIMB LEADS

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THE dramatic benefits to be obtained from modern cardiac surgical procedures have, among other things, crystallized the need for a more accurate diagnosis of heart disease. One of the most elusive of these conditions is right ventricular hypertrophy, and more definite criteria for its recognition are greatly needed. Roentgenologists and clinicians have attacked the problem, but the roentgenographic diagnosis of right ventricular hypertrophy is notoriously difficult and radiologists differ in their opinions as to the reliability of the criteria thought to be of diagnostic importance.¹⁻⁴ Various authors have described the electrocardiographic pattern of marked right ventricular hypertrophy in the standard limb leads⁵⁻¹⁰ and in the precordial leads.^{11-15,27} The criteria for the diagnosis of the lesser degrees of right ventricular hypertrophy have not been clearly established in either standard or precordial leads, nor has the frequency of the significant findings been accurately defined. It is the purpose of this paper to describe the patterns seen in sixty cases of right ventricular hypertrophy and to differentiate normal right axis deviation (due to position of the heart) from abnormal right axis deviation (due to right ventricular hypertrophy).

SUBJECTS AND METHODS

Sixty patients (of whom twenty-four, or 40 per cent, were 5 years of age or younger) with right ventricular hypertrophy who suffered from cyanotic congenital cardiac disease, tetralogy of Fallot, mitral stenosis, cor pulmonale, or kyphoscoliotic disease were studied. Tables I and II summarize the types of cases and the age and sex distribution. Of the forty-four patients with congenital cardiac disease, in twenty the diagnosis was proved by surgical intervention, in six by autopsy, and in seven by Diodrast angiocardigraphy (Table I). The diagnosis in the remainder of the group with congenital cardiac anomalies was made by routine clinical and roentgenographic examination. The diagnosis of right ventricular hypertrophy in patients with chronic asthma and emphysema was based on the clinical manifestations of chronic cor pulmonale with dyspnea

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Aided in part by a grant from the Mrs. Albert E. Schwabacher Fund.

Presented in preliminary form before the American Federation of Clinical Research, April, 1947, Chicago, Ill.

and cyanosis, as well as on the demonstration of emphysema by roentgen examination. Clinical and roentgen examination supplemented the physical signs of mitral stenosis in patients with rheumatic disease.

TABLE I. THE CAUSES OF RIGHT VENTRICULAR HYPERTROPHY IN THE PRESENT SERIES OF CASES

Congenital cardiac disease.....	44
Tetralogy of Fallot.....	18
Proved by autopsy.....	4
Proved surgically.....	13
Proved by Diodrast angiocardiograms.....	1
Cor triloculare with right ventricular hypertrophy; autopsy.....	1
Overriding aorta or high interventricular septal defect with right ventricular enlargement shown by Diodrast angiocardiogram....	6
Miscellaneous cyanotic congenital cardiac disease with abnormal films of the heart but no Diodrast, surgery, or autopsy.....	19
Chronic asthma and emphysema.....	8
Rheumatic heart disease with mitral stenosis.....	6
Kyphoscoliosis.....	1
Pulmonary fibrosis.....	1
	—
Total cases	60

All of the patients were studied by means of standard limb leads, unipolar limb leads, and unipolar precordial Leads V₁ through V₆. On many of the patients further exploratory leads were taken over the right side of the anterior chest, the right side of the upper abdomen, and the xiphoid. Goldberger's modification¹⁶ of Wilson's central terminal was used for the unipolar leads. On all of the patients routine seven-foot films of the chest were taken and on many of the congenital patients Diodrast angiocardiograms were available.*

TABLE II. RIGHT VENTRICULAR HYPERTROPHY; DISTRIBUTION BY AGE AND SEX IN SIXTY CASES

AGE	MALE	FEMALE
1 mo.-2 yrs.	6	7
2 yrs.-5 yrs.	8	3
5 yrs.-10 yrs.	5	2
10 yrs.-20 yrs.	1	4
20 yrs.-30 yrs.	4	4
30 yrs.-50 yrs.	6	4
50 yrs.-70 yrs.	6	0
Total	36	24

The electrocardiograms were analyzed in tabular form on master sheets, all waves of each record being carefully measured through a magnifying lens, if necessary. The amplitude of upright waves was measured from the upper edge

*An independent study by Dr. E. R. Miller and his associates of the Division of Radiology.

of the base line to the peak of the wave; that of inverted waves, from the lower edge. Calibration corrections were applied, if necessary for standardization (1.0 cm. = 1.0 millivolt). In addition to the usual measurements, particular attention was paid to the voltage of the R and S waves in the precordial and unipolar extremity leads in order to calculate the ratios to be described.

One hundred fifty subjects (healthy nurses, medical students, house staff personnel, and flying personnel of a commercial airline, whose histories, physical examinations, electrocardiograms, and roentgenograms of the chest were within normal limits) were used for comparison. The mean age of the normal subjects was 34.6 years, with a range of 4 to 70 years. Four were under the age of 10 years. A separate group of thirteen normal infants from the well-baby clinic were studied for calculation of the R/S ratios and of the ventricular activation time in view of the observations of Battro and Mendy¹⁸ of an abnormally prominent R wave in Lead V_1 in normal infants.

The differentiation of right ventricular hypertrophy and right bundle branch block was attempted and all cases were excluded from this study in which the electrocardiogram showed an M-shaped complex of the QRS with a prominent R wave and a ventricular activation time exceeding 0.07 second in Lead V_1 . This was done to exclude right bundle branch block from the series even though it was appreciated that right ventricular hypertrophy and right bundle branch block could coexist.

RESULTS

Table III summarizes the statistical data obtained in the cases of right ventricular hypertrophy, in the entire normal group, and in subjects with right axis deviation ($+80^\circ$ or more) included in the normal group. Table IV summarizes the criteria obtained from a study of our data for the diagnosis of right ventricular hypertrophy, and Table V summarizes the frequency with which the various electrocardiographic abnormalities were encountered here. It will be seen that abnormalities in voltage and ratios of the R and S waves were the most common abnormalities in the precordial leads.

Voltage of the QRS Complex.—The importance of voltage of the QRS complex is apparent from Table V. No standards of voltage in right ventricular hypertrophy have been published comparable to those of Gubner and Ungerleider¹⁹ in left ventricular hypertrophy.³⁰ The voltage of the R wave and S wave in the present series can be seen in Table III. The mean height of the R wave in Lead V_1 in the normal subjects was 2.3 mm., whereas the mean height of the R wave in right ventricular hypertrophy in V_1 was 9.6 mm., and thirty-five cases (58 per cent) equalled or exceeded the maximum normal R wave of 7.0 millimeters. The mean depth of the S wave in Lead V_1 was 8.6 mm. in the normal group and 3.1 mm. in the cases of right ventricular hypertrophy, and in thirty of these cases (50 per cent) the S wave was less than 2.0 mm. in V_1 . The mean depth of the S wave in V_6 in the normal group was only 0.6 mm. and 6.1 mm. in the cases of right ventricular hypertrophy. In thirty cases (50 per cent) of the latter, the S wave equalled or exceeded the maximum normal of 7.0 mm. in V_5 and/or V_6 .

TABLE III. THE VENTRICULAR DEFLECTIONS IN THE UNIPOLAR LIMB AND PRECORDIAL LEADS (MEASUREMENTS IN MILLIMETERS)

LEAD	RIGHT VENTRICULAR HYPERTROPHY (60 CASES)					NORMAL (150 CASES)					NORMAL—RIGHT AXIS DEVIATION (19 CASES)				
	MEAN	ST. DEV.	MIN.	MAX.		MEAN	ST. DEV.	MIN.	MAX.		MEAN	ST. DEV.	MIN.	MAX.	
V ₁ Q R S T VAT*	0.07	0.25	(0.0	1.0)		0.0	0.0	(0.0	0.0)		0.0	0.0	(0.0	0.0)	
	9.6	7.6	(0.0	28.0)		2.3	1.5	(0.0	7.0)		2.1	1.6	(0.0	7.0)	
	3.1	4.1	(0.0	19.0)		8.6	4.3	(2.0	25.0)		8.4	4.3	(1.5	17.0)	
	-1.09	7.77	(-5.0	+ 5.5)		0.15	1.58	(-4.0	+4.0)		-0.26	1.06	(-1.5	+3.0)	
	0.04	0.06	(0.0	0.08)		0.02	0.007	(0.0	0.03)		0.02	0.008	(0.0	0.03)	
V ₂ Q R S T VAT*	0.0	0.0	(0.0	0.0)		0.0	0.0	(0.0	0.0)		0.0	0.0	(0.0	0.0)	
	9.4	7.1	(0.5	25.0)		5.9	3.1	(0.0	16.0)		5.9	2.8	(2.0	11.0)	
	10.0	6.5	(0.5	24.0)		12.7	5.3	(0.0	29.0)		15.4	5.0	(4.0	29.0)	
	2.2	6.78	(-6.0	+8.0)		5.2	3.32	(-3.0	+18.0)		4.6	2.34	(+1.5	+11.0)	
	0.03	0.01	(0.0	0.08)		0.025	0.006	(0.0	0.04)		0.024	0.008	(0.015	0.04)	
V ₃ Q R S T VAT*	0.01	0.07	(0.0	0.5)		0.01	0.06	(0.0	0.5)		0.0	0.0	(0.0	0.0)	
	10.1	7.2	(1.0	33.0)		8.9	4.3	(1.5	26.0)		7.4	2.6	(3.0	13.0)	
	10.2	6.0	(0.5	22.0)		8.8	5.3	(0.0	25.0)		11.3	5.7	(2.0	25.0)	
	2.6	6.85	(-7.0	+10.0)		5.38	2.96	(-2.0	+16.0)		5.18	2.21	(+2.0	+10.0)	
	0.03	0.01	(0.0	0.07)		0.03	0.007	(0.02	0.04)		0.029	0.007	(0.015	0.04)	
V ₄ Q R S T VAT*	0.15	0.92	(0.0	6.5)		0.1	0.4	(0.0	3.0)		0.03	0.02	(0.0	0.5)	
	10.0	7.8	(1.0	35.0)		14.2	5.5	(4.0	27.0)		13.4	4.4	(4.0	23.0)	
	10.4	6.3	(1.0	23.0)		5.2	4.0	(0.0	20.0)		6.5	5.0	(0.0	19.0)	
	2.7	6.84	(-9.5	+11.0)		4.8	2.76	(0.0	+17.0)		4.18	1.79	(+1.0	+8.0)	
	0.03	0.01	(0.0	0.05)		0.034	0.007	(0.02	0.05)		0.032	0.007	(0.02	0.04)	

V_4	Q R S T VAT*	0.31 7.9 8.5 2.4 0.03	0.98 6.1 5.6 7.33 0.01	(0.0 5.0 30.0 -9.0 0.0) (0.0 0.05)	0.3 12.1 1.5 3.43 0.04	0.6 4.4 1.5 1.62 0.01	(0.0 4.0 26.0 0.0 0.0) (0.0 0.05)	0.2 10.2 2.0 3.29 0.035	0.1 3.7 1.8 1.49 0.008	(0.0 4.0 0.0 +2.0 0.02) (0.02 0.04)
V_6	Q R S T VAT*	0.4 6.6 6.1 2.2 0.03	1.1 6.1 4.8 7.89 0.01	(0.0 0.5 32.0 0.0 -1.0) (0.0 0.05)	0.4 9.2 0.6 2.43 0.04	0.5 3.6 1.0 1.11 0.01	(0.0 4.0 22.0 0.0 -0.5) (0.02 0.05)	0.3 8.1 0.8 2.37 0.03	0.2 3.6 0.9 1.01 0.01	(0.0 2.5 0.0 +1.5 0.02) (0.02 0.05)
aV_L	Q R S T	0.28 2.7 6.0 0.3	0.81 2.7 3.6 8.73	(0.0 0.0 10.0 0.0 -3.0) (0.0 0.05)	0.2 2.1 0.4 0.53	0.5 2.1 3.9 1.26	(0.0 0.0 10.0 0.0 -4.0) (0.0 0.05)	0.1 0.9 0.5 0.45	0.2 0.8 3.6 1.0	(0.0 0.0 0.0 -2.0 0.05) (0.0 0.05)
aV_R	Q R S T	2.1 3.9 1.5 -1.8	2.5 2.9 2.8 8.78	(0.0 0.0 14.0 0.0 -4.0) (0.0 0.05)	2.0 0.8 4.3 -2.31	3.7 0.9 4.0 0.92	(0.0 0.0 5.0 13.0 -5.0) (0.0 0.05)	1.8 0.8 4.3 -2.08	2.7 0.8 4.6 0.84	(0.0 0.0 0.0 -4.0 0.05) (0.0 0.05)
aV_F	Q R S T	0.36 3.9 1.5 1.3	0.66 2.9 2.8 8.47	(0.0 0.0 14.0 0.0 -2.5) (0.0 0.05)	0.5 1.3 0.2 1.86	1.4 8.3 1.3 1.1	(0.0 0.0 20.0 0.0 -0.5) (0.0 0.05)	0.7 10.5 0.4 1.84	0.2 4.2 2.1 0.96	(0.0 0.7 0.0 +0.5 0.05) (0.0 0.05)

*Ventricular activation time in seconds; measured from the beginning of the QRS complex to the peak of the R wave.

TABLE IV. THE CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY AS OBTAINED BY A STUDY OF SIXTY CASES

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- I. Voltage of the R and S waves and various ratios:
 1. The R wave in V_1 is 7.0 mm. or more.
 2. The S wave in V_1 is less than 2.0 millimeters.
 3. The S wave in V_5 or V_6 is 7.0 mm. or more.
 4. The sum of the amplitudes of the R wave in V_1 and the S wave in V_5 and V_6 exceeds 10.5 mm. in individuals over 5 years of age.
 5. The R wave in V_5 or V_6 is less than 5.0 millimeters.
 6. The ratio of the R to the S wave in V_5 or V_6 is 1.0 or less.
 7. The R wave in aV_R is 5.0 mm. or more.
 8. The ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.4 or less.
 9. The ratio of the R wave in V_1 to the S wave in V_1 exceeds 4.0 in individuals under the age of 5.
 10. The ratio of the R wave to the S wave in V_1 exceeds 1.0 in individuals over the age of 5 years.
 - II. Delayed onset of the intrinsicoid deflection (delayed ventricular activation time) 0.04 to 0.07 second in V_1 and/or V_2 .
 - III. Depression of the RS-T segment and inversion of the T wave in:
 - a. V_1 , less often V_2 and V_3 when the R wave equals or exceeds 5.0 millimeters.
 - b. aV_L or aV_F when the R wave equals or exceeds 5.0 millimeters.
 - IV. Marked right axis deviation, greater than $+110^\circ$ suggests, but is not in itself diagnostic of, right ventricular hypertrophy.
-

The mean height of the R wave in V_5 in the normal group was 12.1 mm., as contrasted to 7.9 mm. in the cases of right ventricular hypertrophy, and in twenty-one cases (36 per cent), the R wave was 4.0 mm. or less. The mean height of the R wave in aV_R was 0.8 mm. in the normal subjects and 3.9 mm. in the cases of right ventricular hypertrophy. Of the latter, the voltage of the R wave in aV_R equalled or exceeded the maximum normal of 5.0 mm. in eighteen cases (30 per cent).

In addition to the absolute value of the height of the R wave and depth of the S wave, the relationship of the R wave to the S wave in V_1 and in V_5 and V_6 was found to be quite different in the group with right ventricular hypertrophy, as compared with the normal subjects (Table VI). Calculations of the R/S ratio in Lead V_5 from data on nine cases of chronic pulmonary heart disease from the paper by Salazar and Sodi-Pallares²⁰ revealed a mean R/S ratio of 0.94. In six of the nine cases, the R/S ratio in V_5 was less than 0.6, in contrast to the minimum normal in our series of 1.0. The difference between the two groups

was more strikingly evident when the ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ was determined (Table

VII). The mean figure for this latter ratio was 1.6 in the cases of right ventricular hypertrophy, as compared with 32 in the normal subjects. In fifteen (48 per cent)

of the thirty-one cases of right ventricular hypertrophy in which the ratio could be calculated, the ratio $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ equalled or was less than the minimum normal value of 0.4. The sum of the total right ventricular potentials R wave in V_1

TABLE V. THE FREQUENCY OF VARIOUS ABNORMALITIES OF THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY

I. Voltage of the R and S waves.....	53
R wave in V_1 , 7.0 mm. or more	35
S wave in V_1 , less than 2.0 mm.	30
S wave in V_5 or V_6 , 7.0 mm. or more	30
R in V_1 + S in V_5 exceeds 10.5 mm. in individuals over 5 years	26
R wave in V_5 or V_6 , 4.0 mm. or less	21
R/S ratio, 1.0 or less in V_5 or V_6	19
R wave in aV_R is 5.0 mm. or more	18
The ratio $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.04 or less	15
The R/S ratio* exceeds 4.0 in patients under 5 years	9
The R/S ratio* exceeds 1.0 in patients over 5 years	8
II. Delayed onset of the intrinsicoid deflection (right ventricular activation time), 0.04 second to 0.07 second.....	42
III. Axis deviation between $+110^\circ$ and -80°	37
IV. Abnormalities of the RS-T segment and T wave.....	30
Inverted T wave in V_1 with R wave 5.0 mm. or more	26
Inverted T wave in V_1 , V_2 , and V_3	9
Inverted T wave in V_1 and V_2	6
Inverted T wave in standard Leads II and III	6
Inverted T wave in Lead aV_L when associated with R wave greater than 5.0 mm.	4
V. Tall P waves (greater than 2.5 mm.) in standard Leads II and III or unipolar Leads V_5 , V_6 , or aV_F	9

*These ratios can be calculated only when R and S waves are both present.

TABLE VI. THE R/S RATIO IN RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

LEAD	NORMAL				RIGHT VENTRICULAR HYPERTROPHY			
	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.
V_1	0.3	0.3	(0.0	1.0)	3.1	6.3	(0.0	28.0)
V_2	0.2	1.2	(0.1	13.0)	2.1	3.1	(0.0	16.0)
V_3	1.4	1.4	(0.1	10.0)	1.9	2.4	(0.0	12.0)
V_4	4.1	3.8	(0.2	19.0)	1.6	1.7	(0.1	7.0)
V_5	7.3	4.7	(1.0	24.0)	1.4	2.4	(0.1	16.0)
V_6	9.0	5.0	(2.3	22.0)	2.1	4.5	(0.0	28.0)

TABLE VII. THE R/S IN V_5 DIVIDED BY THE R/S RATIO IN V_1 IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

	$\frac{R/S \text{ IN } V_5}{R/S \text{ IN } V_1}$			
	MEAN	ST. DEV.	MIN.	MAX.
Right ventricular hypertrophy	1.61	2.26	(0.01	8.5)
Normal subjects	32.0	26.9	(0.4	100.0)

+ S wave in V_5 or S wave in V_6 proved to be significant (Table VIII). The mean sum of the amplitude of R in V_1 + S in V_5 or S in V_6 in the cases of right ventricular hypertrophy was 16.1 mm., as compared with a value of 3.7 mm. in the normal adult subjects. In twenty-six cases (out of thirty-six) of right ventricular hypertrophy over the age of five years, the sum exceeded the maximum normal value of 10.5 millimeters. In two normal children, both 5 years of age, the sum of R in V_1 plus S in V_5 equalled 15 millimeters. In only three normal subjects over the age of 5 did the sum of R in V_1 plus S in V_5 exceed 7.0 millimeters.

TABLE VIII. THE SUM OF THE AMPLITUDES OF THE R WAVE IN S_1 AND THE S WAVE IN S_5 OR V_6 (WHICHEVER IS GREATER) IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

	R WAVE IN V_1 + S WAVE IN V_5 OR S WAVE IN V_6			
	MEAN	ST. DEV.	MIN.	MAX.
Right ventricular hypertrophy	16.1	9.0	(4.0	37.0)
Normal subjects	3.7	2.4	(0.0	10.5)

In four cases of chronic cor pulmonale with normal voltage of the R wave and normal ventricular activation time in V_1 , but with an abnormal R/S ratio in V_5 , the sums equalled 11, 12, 13, and 14 mm., respectively (Fig. 7). A calculation of the total right ventricular potential from the data presented on twelve cases of chronic cor pulmonale published by Salazar and Sodi-Pallares²⁰ revealed that in four (30 per cent) the sum of R in V_1 and S in V_5 exceeded our maximum normal value of 10.5 millimeters. These data suggest that the voltage of the right ventricular potentials may be an important associated criterion of right ventricular hypertrophy and may be especially valuable in borderline cases.

The R/S ratio in V_1 in thirteen normal infants under the age of 2 years was determined and found to be conspicuously greater than that seen in the group of older normal subjects, but was never greater than 4. In these normal infants,

the ventricular activation time* in V_1 did not exceed 0.02 second, despite an R/S ratio of 3 or 4. As will be seen later, this is in distinct contrast to the cases of right ventricular hypertrophy, in which an increased ventricular activation time was found in V_1 when the R/S ratio was of this magnitude. The R/S ratio in V_5 and V_6 in the normal infants did not differ significantly from that seen in the normal adults, again in contrast to what was found in the cases of right ventricular hypertrophy.

*Ventricular Activation Time** (time of onset of the intrinsicoid deflection).—The data in Table III indicate that the time of onset of the intrinsicoid deflection in relation to the onset of the QRS complex in Lead V_1 (ventricular activation time) is occasionally of definite value in the diagnosis of right ventricular hypertrophy. In four different series of normal subjects comprising 332 cases,^{17,21,22,29} the onset of the intrinsicoid deflection (ventricular activation time) in V_1 was less than 0.04 second. Kossmann and Johnston²¹ stated that the time of onset of the intrinsicoid deflection in the normal individual averages 0.02 second in V_1 . In the present control series of normal subjects the upper limit of normal found in Lead V_1 was 0.03 second. This is in contrast to the cases of right ventricular hypertrophy of which 42 per cent of the total revealed a ventricular activation time of 0.04 second or more, but less than 0.07 second in V_1 . Delay in the ventricular activation time was found in practically all of the proved cases of pulmonary stenosis (Figs. 1, 2, and 4), in some of the cases of mitral stenosis (Fig. 5), but rarely in the cases of chronic cor pulmonale (Fig. 7). In some instances of right ventricular hypertrophy, notching of the upstroke of the R wave occurred in V_1 (Fig. 2) and suggested the presence of an associated conduction defect, but in these cases, the ventricular activation time in V_1 was less than 0.06 second, and broad, slurred S waves in the left precordial leads were absent. The possibility of an associated right bundle branch block was considered when the ventricular activation time in V_1 exceeded 0.07 second; cases of this type have been excluded from this study. The right ventricular activation time may not be delayed in the marked right ventricular hypertrophy of pulmonary stenosis or related lesions if dextrocardia is also present (Fig. 3). In the cyanotic child whose tracing is shown in this figure, the bizarre axis, the abnormalities in the unipolar extremity leads, and the RS ratio in V_6 lead to the correct ante-mortem diagnosis of right ventricular hypertrophy.

RST-T Abnormalities.—In contrast to their frequency in left ventricular hypertrophy, abnormalities of the RS-T segment and T waves in the unipolar precordial and extremity leads were seen less frequently and were of less diagnostic value in right ventricular hypertrophy than the abnormalities of voltage and ventricular activation time. Earlier workers emphasized the importance of a depression of the RS-T segments with inversion of the T waves in Leads II and III in the diagnosis of right ventricular hypertrophy.⁵⁻¹⁰ In the cases of the present series, these RST-T changes were seen inconsistently in Leads II and III (Table III). Depression of the RS-T segment and inversion of the T

*The time in seconds from the onset of the QRS complex to the beginning of the abrupt downstroke of the R wave.

waves, when present in the extremity leads, was seen more frequently in the left leg lead (aV_F) and more rarely found in the left arm lead (aV_L) (Figs. 4 and 7). The characteristic RST-T contour of ventricular hypertrophy with depressed convex RS-T segment and asymmetrically inverted T wave was seen more frequently in the right precordial leads than in the extremity leads. When the

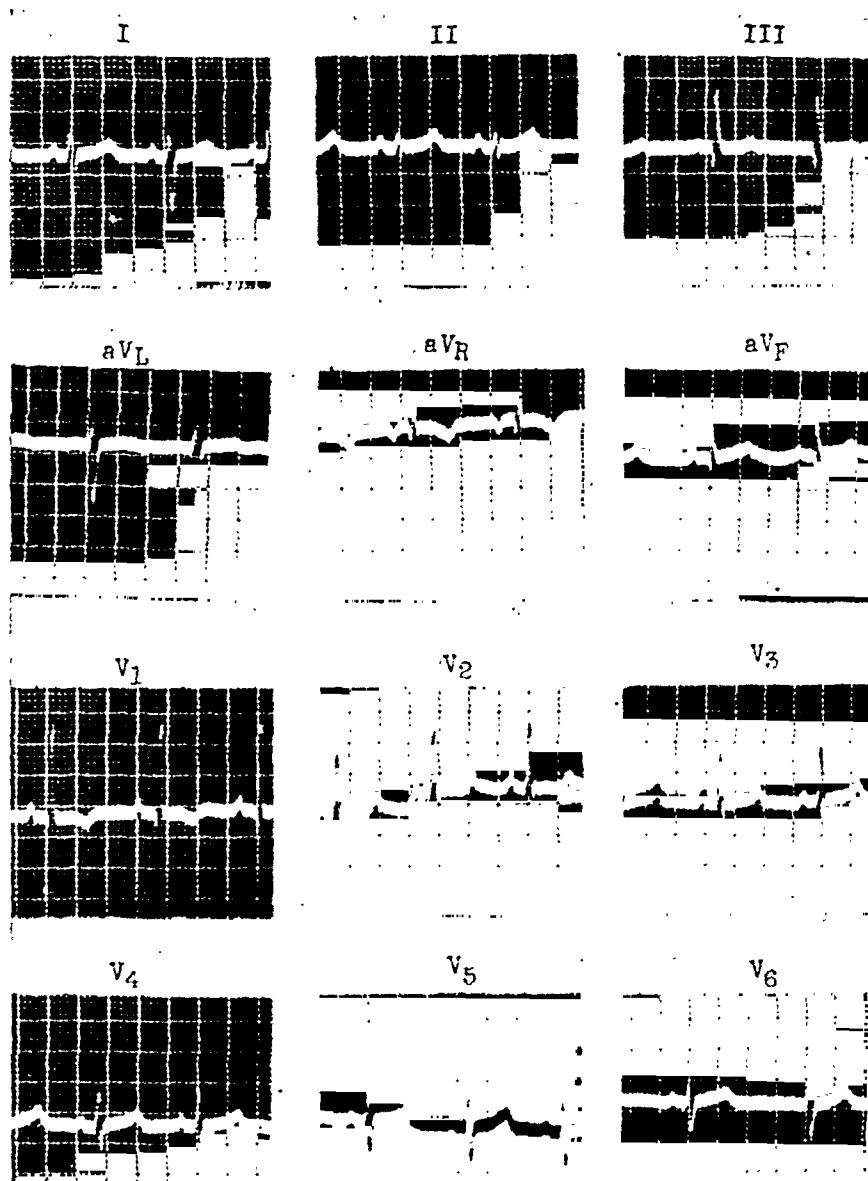


Fig. 1.—S. Z., boy, age 7, U133502. Tetralogy of Fallot. Blalock operation with excellent results. Tracing shows typical finding of right ventricular hypertrophy with marked right axis deviation, tall R wave, absent S wave, delayed ventricular activation time, slightly depressed R-ST segment and inverted T wave in V_1 , and small R and deep S wave with short ventricular activation time in V_5 and V_6 .

RST-T complex was normal in the standard and extremity leads (Figs. 1 and 2), characteristically tall R waves with delayed ventricular activation time and abnormal RST-T findings occasionally were seen in Leads V_1 and V_2 . Inverted T waves in V_1 through V_3 appeared occasionally as the sole electrocardiographic manifestation of acute cor pulmonale (acute pulmonary embolism).

The RST-T abnormalities were first seen either in Lead V_1 or in the unipolar extremity leads. When the left leg lead was abnormal, RST-T abnormalities were usually found in standard Leads II and III (Figs. 4 and 7).

Table IX summarizes the relationship of the T wave to the height of the R wave in patients with right ventricular hypertrophy as compared with the normal subjects.

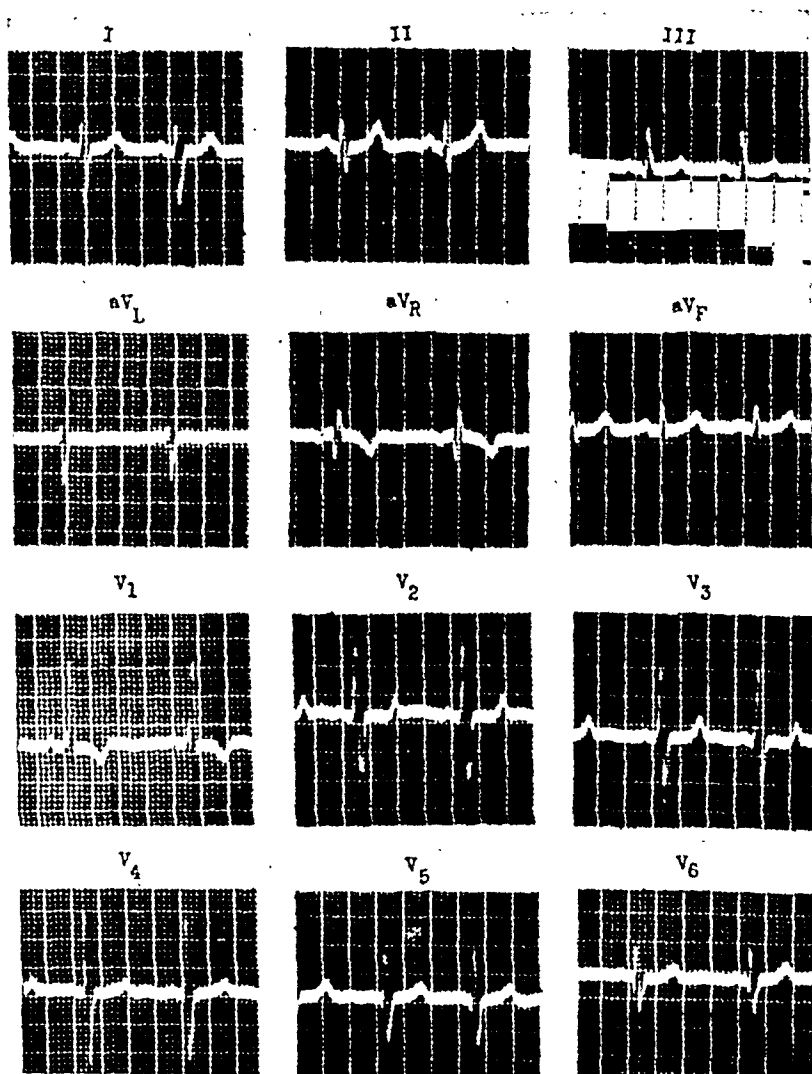


Fig. 2.—F. L., boy, age 7, U132040. Pulmonary atresia with marked right ventricular hypertrophy proved at autopsy. Note the typical findings of right ventricular hypertrophy. Lead V_1 reveals the typical abnormalities, whereas V_2 is not abnormal.

P-Wave Abnormalities.—Abnormalities of the P wave have been noted frequently in right ventricular hypertrophy. Katz¹⁰ has referred to the so-called "P pulmonale pattern" in which large P waves occur in Leads II and III. Salazar and Sodi-Pallares²⁹ also emphasized the importance of abnormal P waves in Leads II, III, and aV_F in chronic cor pulmonale. Our data (Table V) show the occasional presence of these findings, although we have not diagnosed right ventricular

TABLE IX. THE RATIO OF THE R WAVE TO THE T WAVE (R/T RATIO) IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

LEAD	NORMAL				RIGHT VENTRICULAR HYPERTROPHY			
	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.
V ₁	1.4	0.9	(0.3	7.0)	3.9	3.1	(0.5	11.0)
V ₂	1.4	1.4	(0.2	12.0)	3.3	2.9	(0.2	11.0)
V ₃	1.9	1.6	(0.3	13.0)	3.1	2.9	(0.1	15.0)
V ₄	2.9	1.7	(0.3	9.0)	3.4	3.3	(0.1	17.5)
V ₅	3.5	1.6	(1.0	9.0)	3.0	2.2	(0.6	10.0)
V ₆	4.1	1.9	(1.7	10.0)	2.6	1.6	(0.8	7.0)
VL	2.6	1.9	(0.1	10.0)	2.6	2.1	(0.5	8.0)
VF	4.6	3.2	(0.3	14.0)	4.2	2.7	(0.7	10.0)

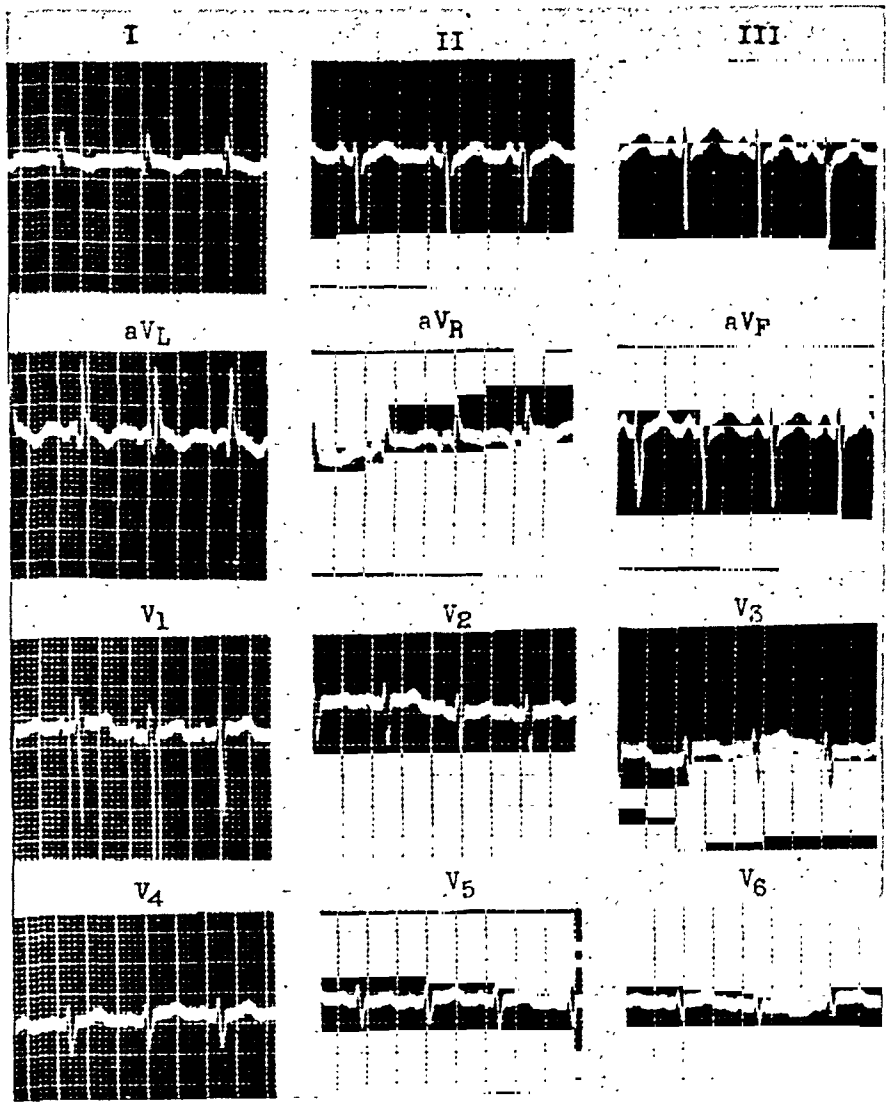


Fig. 3.—R. C., boy, age 10 months, U133966. Hypoplastic pulmonary artery, interauricular septal defect, dextrocardia, and marked right ventricular hypertrophy proved at autopsy. The dextrocardia explains the bizarre axis and absence of typical findings in Lead V₁.

hypertrophy solely on the basis of the P-wave abnormalities, nor do we recommend such a procedure. Tall, peaked P waves, rather than broad, notched P waves were the usual variation from normal seen in both the chronic cor pulmonale group (Figs. 6 and 7) and in the patients with congenital cardiac disease. In mitral stenosis, however, broad or notched P waves were the usual finding (Fig. 5).

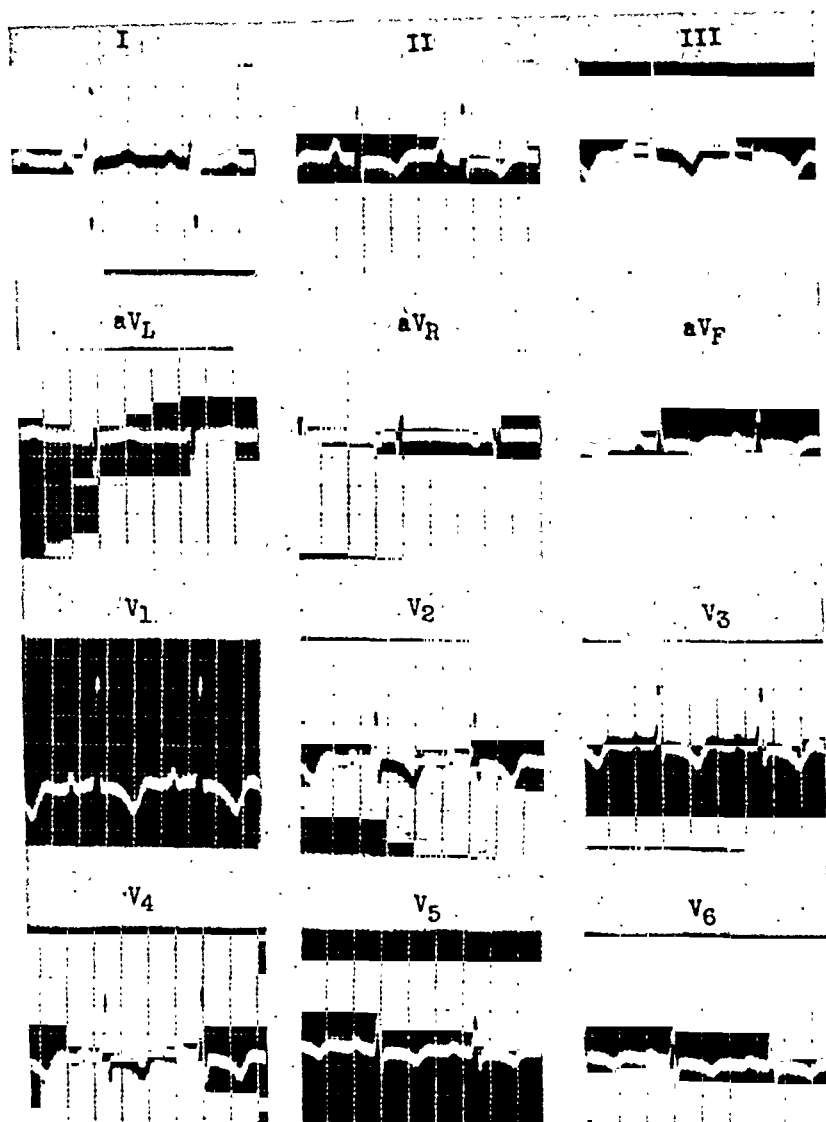


Fig. 4.—L. C., woman, age 25, U134697. Pulmonary stenosis and patent interauricular septal defect with right ventricular hypertrophy proved at autopsy. Right ventricular thickness, 1.5 cm.; left ventricular thickness 1.1 cm. Normal coronary arteries.

Electrocardiographic Position of the Heart.—The electrocardiographic position of the heart, using the criteria of Wilson and his associates,¹² was frequently indeterminate. A horizontal position was noted on occasion, but often neither the right nor the left precordial leads in any way resembled the electrocardiographic patterns of the left leg or the left arm leads. At times, the right pre-

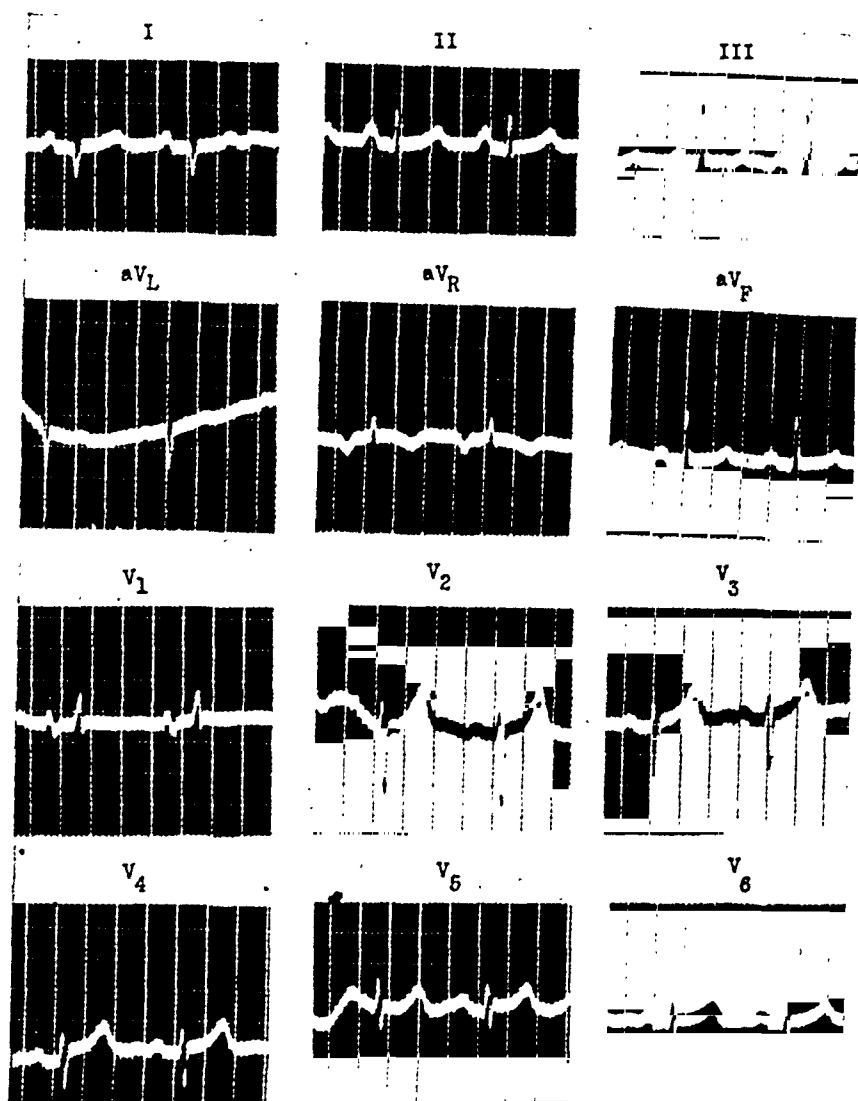


Fig. 5.—G. T., woman, age 29. Mitral stenosis. Note the abnormal P waves in Leads II, III, and aVF, the monophasic upright R wave in aVR, the broad negative phase of the P wave in V₁, and the R/S ratio in V₁ with a ventricular activation time of 0.04 second. The R/S ratio in V₁ is definitely abnormal, whereas that in V₂ is quite normal.

cordial leads most closely resembled the pattern seen in the right arm lead, suggesting that rotation of the heart had occurred in such a manner as to allow the right ventricle to face the right arm. Variations in the pattern of right ventricular hypertrophy in the standard leads due to variable position of the heart were seen less frequently than in left ventricular hypertrophy.³⁰ The electrical axis was calculated according to the method of Carter and his associates²³ and the findings tabulated. It was found that practically all patients with congenital cardiac disease with marked right ventricular hypertrophy had a marked right axis deviation, usually greater than $+120^\circ$, and at times ranging into bizarre axes such as -160 degrees. The axes obtained in the lesser degrees of right ventricular hypertrophy, such as were found in mitral stenosis and chronic cor pulmonale, fell into the range of the upper limits of normal, so that axis deviations of $+80^\circ$ to $+110^\circ$ were noted frequently in these cases.

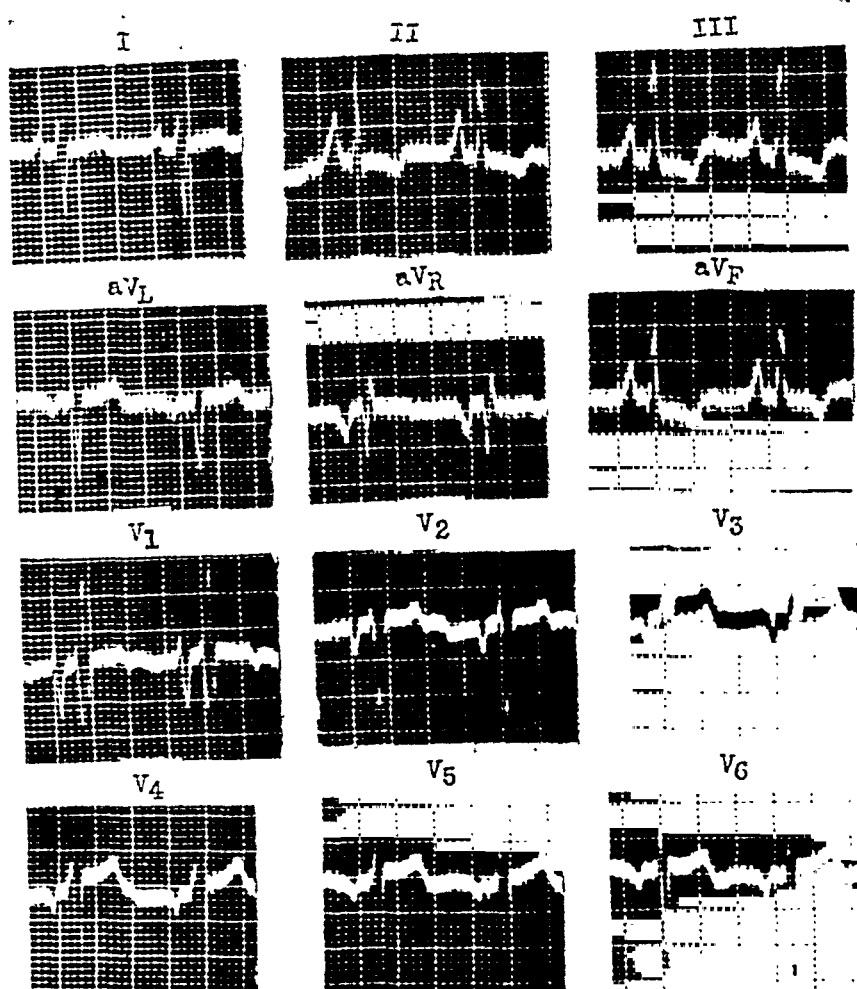


Fig. 6 (Courtesy of Dr. Mervin J. Goldman, Veterans Administration Hospital, Oakland, Calif.).—V. H. S., a man, age 60. Increasing cough, sputum, and dyspnea for twelve years. On admission, right heart failure. Autopsy showed diffuse pulmonary fibrosis, emphysema, and bronchiolectasis. Right ventricular wall, 10 mm; left ventricular wall, 10 mm.; heart weight, 460 grams.

DISCUSSION

It is apparent that the electrocardiographic findings are reliable and consistent in the well-marked case of right ventricular hypertrophy such as occurs in pulmonary stenosis or tetralogy of Fallot (Figs. 1, 2, and 4). Such hypertrophy can be strongly suspected if the electrical axis in the standard limb leads is greater than $+110$ degrees. Definitive criteria, however, required a study of Leads V_1 , V_5 , and occasionally aV_R . Abnormal findings in Lead aV_R were rarely observed unless diagnostic changes were also seen in Leads V_1 and/or V_5 . In the eighteen cases of congenital cardiac disease verified at surgery or autopsy, all had the typical findings of right ventricular hypertrophy in Leads V_1 , V_5 , and aV_R (Figs. 1, 2, and 5).

The differentiation of normal from abnormal right axis deviation is of clinical importance and cannot reliably be made from the standard leads alone, even

though the electrical axis is greater than $+110^\circ$, and abnormalities of the RS-T segment and T waves occur in Leads II and III. The unipolar extremity leads have proved of value in this differentiation by indicating a normal vertical position of the heart to explain the right axis deviation (Fig. 8). However, when individuals with cardiac lesions, such as mitral stenosis, were found to have vertically placed hearts and right axis deviation, further study was required with unipolar precordial and limb leads to determine whether the axis deviation was

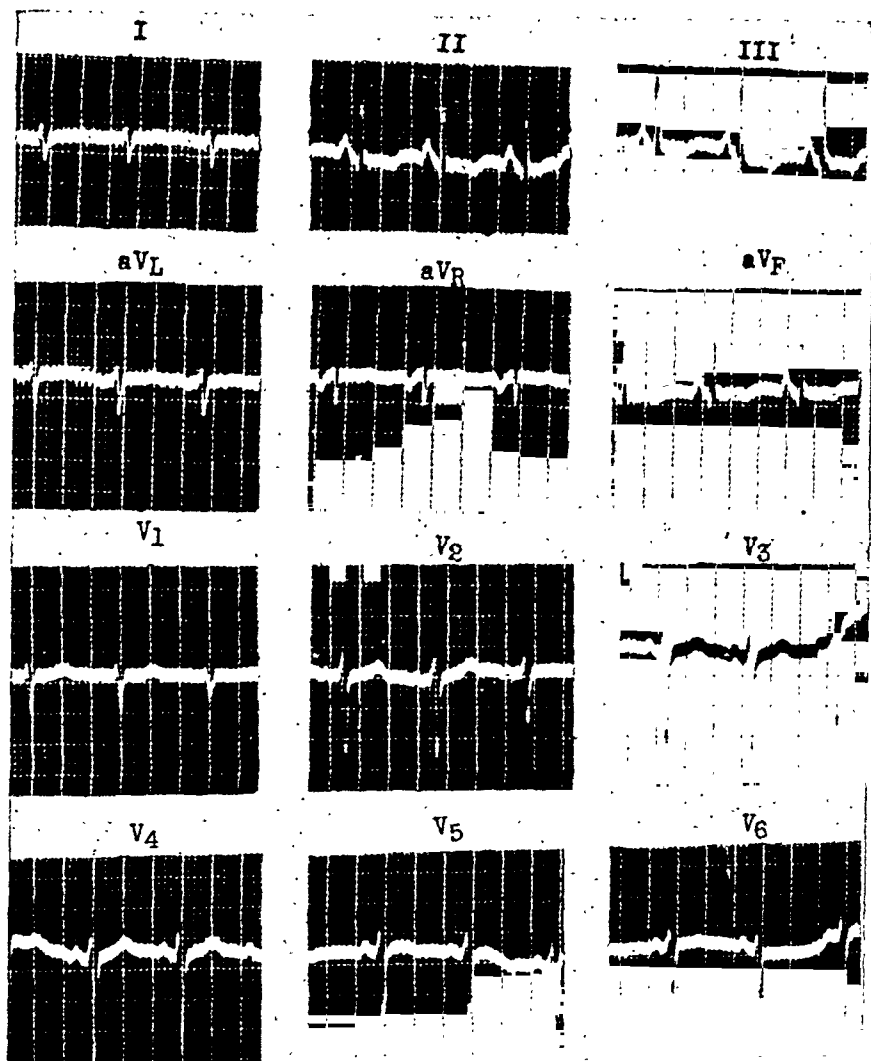


Fig. 7.—W. D., man, age 34, U134878. Chronic asthma, emphysema, and cor pulmonale. Note the abnormal RST-T complex in Leads aVR, II, and III with the low, upright T wave in aVR. The very small R in V₅ and V₆ with a deep S wave in these leads is abnormal. The R wave in V₁ plus the S in V₅ equals 11 millimeters.

due to right ventricular hypertrophy or to a vertical heart with a clockwise rotation on its longitudinal axis. The precordial leads were most helpful in this situation since none of the findings characteristic of right ventricular hypertrophy were observed in these leads in normal subjects with vertical hearts and right axis deviation. Leads V₁ and V₅ were of especial value, and from the changes in these leads the diagnosis was made in most cases. The importance of establishing the diagnosis of right ventricular hypertrophy in individuals with cardiac

lesions which put a strain on the right side of the heart is clear. As Katz¹⁰ stated: "The presence of right ventricular hypertrophy indicates that an acoustically evident valvular lesion has become dynamically important." The prognosis is therefore less favorable.

It is not clear why the predominant features of right ventricular hypertrophy should often be seen solely in Lead V_1 and less often in V_2 as well (Figs. 1, 2, and 5) since the clockwise rotation of the heart in right ventricular hypertrophy

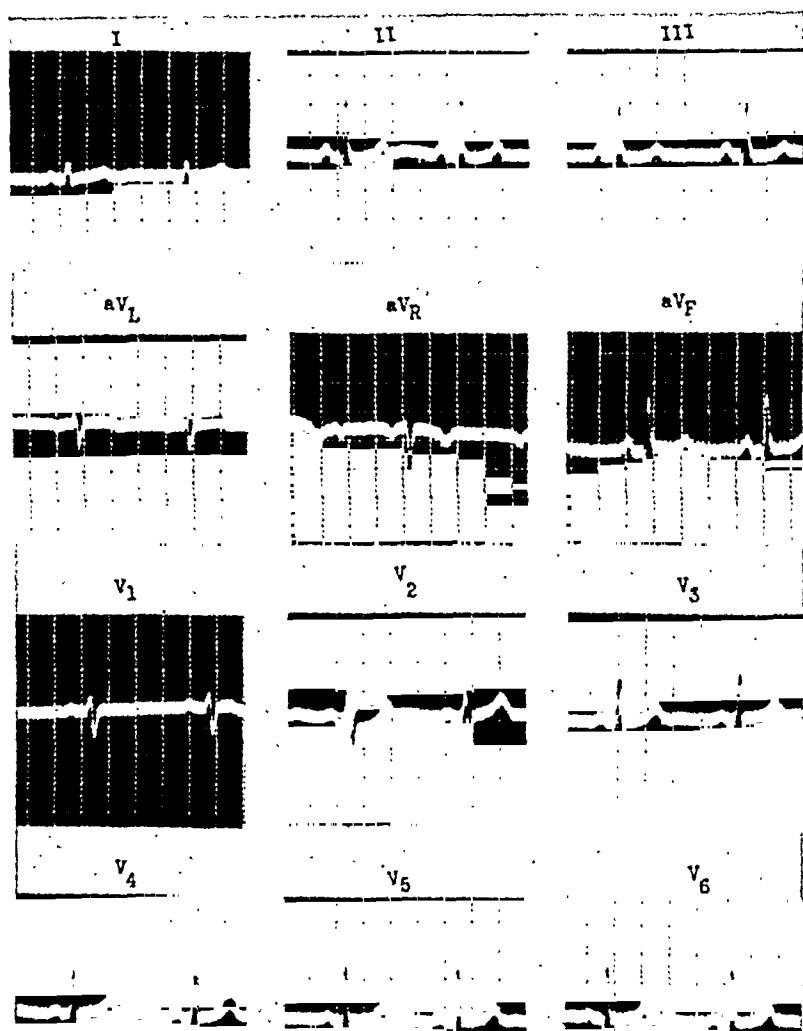


Fig. 8.—B. P., woman, age 22, U111442. Axis +85. Normal vertical heart.

allows the right ventricle to present as the major portion of the anterior cardiac surface. But in precordial Positions 3 and 4, despite the fact that the exploring electrode is presumably over the right ventricle, patterns similar to those from the left ventricle have been obtained (Fig. 2). This is of practical importance because some clinics utilize Position 2 as the site for recording the routine right precordial lead. If right ventricular hypertrophy is suspected, Lead V_1 should

be taken, because often V_2 is not abnormal (Fig. 2) and the diagnosis of right ventricular hypertrophy would then be dependent largely on the changes in V_5 and V_6 , leads which give signs of lesser reliability (Figs. 6 and 7).

A study of the electrocardiographic position of the heart has revealed errors in the diagnosis of ventricular hypertrophy. Earlier authors have described the combination of right axis deviation and inverted T wave in standard Leads II and III as typical of right ventricular hypertrophy.⁵⁻¹⁰ However, we have noted cases of *left* ventricular hypertrophy in vertical hearts, where the same combination of findings may be present in the standard limb leads (Fig. 9). This fact has been described clearly by Wilson and his associates,¹² but apparently has not been sufficiently appreciated. Study of the precordial leads in these cases will reveal the changes in V_5 and V_6 as being the result of left and not right ventricular hypertrophy, and the left leg lead will show the findings seen in left ventricular hypertrophy. Since the abnormal RST-T changes appear in Lead aV_F , they usually also appear in Leads II and III. In occasional cases, the RS-T abnormalities may appear only in Lead aV_F . The right axis deviation is due to the vertical position of the heart. Left ventricular hypertrophy can be suspected in these circumstances because the S wave in Lead I may be small or absent and the R wave is usually tall in Leads II and III (Fig. 9). The precordial leads, however, are required for the definitive diagnosis.³⁰

The frequency of right ventricular hypertrophy in chronic pulmonary disease (as determined by autopsy) has been stressed,^{24,25,26} and yet the clinical diagnosis of right ventricular hypertrophy has been difficult to establish. Our results suggest that calculation of the various ratios and reference to the data on voltage presented may be helpful in diagnosis. Salazar and Sodi-Pallares²⁰ in a recent study of fourteen cases of chronic pulmonary heart disease have commented on the frequency of normal findings in Leads V_1 and V_2 in this group of cases and the fact that reliance for diagnosis must be placed on abnormalities found in Leads V_5 and V_6 and on the abnormal P-wave pattern. Care must be taken that precordial leads are taken sufficiently far to the left in order to be well past the transitional zone before a small R and prominent S wave in Leads V_5 or V_6 are interpreted as supportive evidence for right ventricular hypertrophy. In patients with marked clockwise rotation of the heart, a prominent S wave may be present over a transitional zone which occasionally is displaced as far to the left as Position 6 or rarely 7. A small R wave may be found over the fringes of a myocardial infarct, but here a deep S wave is rarely seen.

Further study is required in infants and in cases of early right ventricular hypertrophy due to cor pulmonale and mitral stenosis in order to establish the reliability of these criteria when the variations from normal occur solely in the left precordial leads.

Myers and his associates²⁸ have published very recently an excellent paper on the electrocardiographic criteria of right ventricular hypertrophy based on forty autopsied cases. This paper appeared just as the final draft on our paper was being prepared. Myers and his associates emphasized the importance of the R/S ratios in the right and left precordial leads, the ventricular activation time,

the inversion of the T wave in Lead V₁, and the fact that incomplete or complete right bundle branch block may be associated with right ventricular hypertrophy. They noted the need for considering the possibility of abnormal displacement of the transitional zone to the right or to the left before attributing the findings to hypertrophy of the right ventricle. They also emphasized the relative diagnostic inadequacy of the pattern of a depressed RS-T segment in Leads II and III and inversion of the T wave in these leads, findings that for so long have been considered the basic pattern for right ventricular hypertrophy.

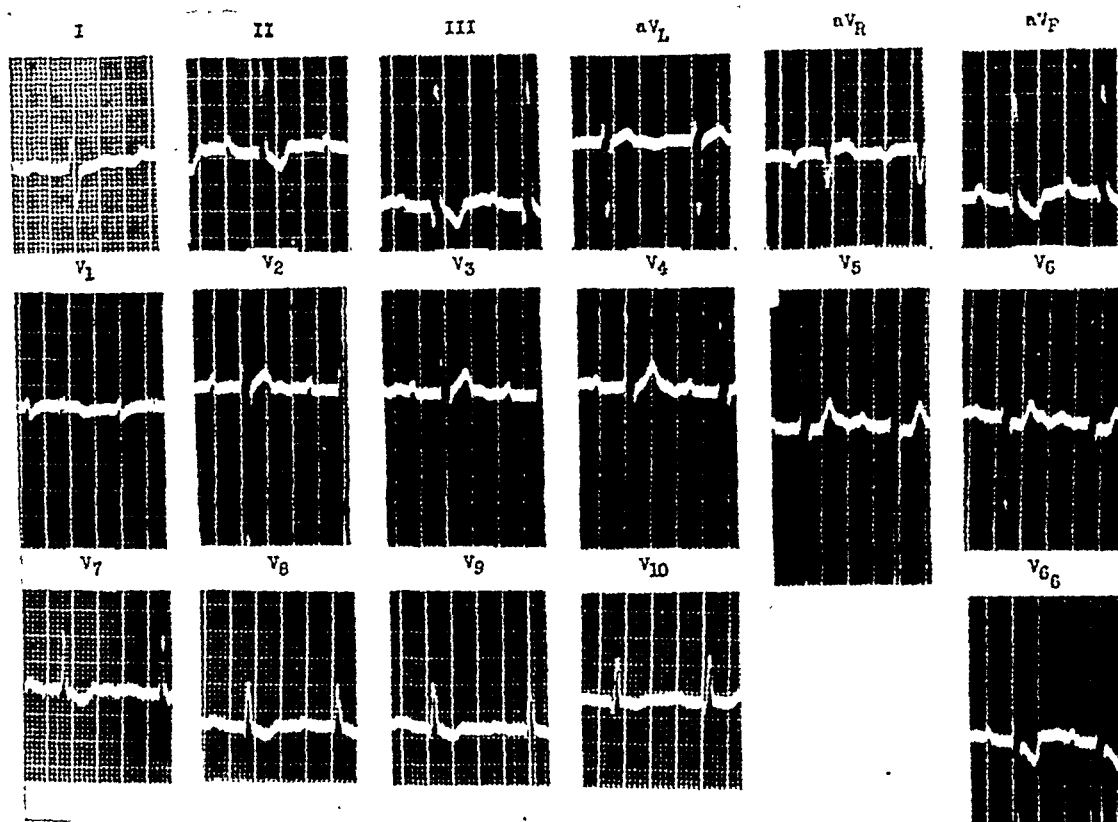


Fig. 9.—M. S., a woman, age 30. Congenital heart disease with large pulmonary artery and left ventricular hypertrophy confirmed by Diodrast angiocardigram. Right axis deviation with inverted T₂ and T₃ plus the deep S in V₆ suggested right ventricular hypertrophy, but the abnormalities in aV_F indicated the need for further left precordial exploratory leads. Leads V₇ to V₁₀ and V_{6G} in the sixth intercostal space indicated left ventricular hypertrophy with displacement of the transitional zone to Position 7.

The detailed data given by Myers and his associates on forty autopsied cases with right ventricular hypertrophy in Table II of their paper²⁸ were used to determine the reliability of the criteria which we have compounded from a study of our sixty cases. Of the thirty-three cases in Groups A through E of their classification, all would have been diagnosed as right ventricular hypertrophy by our criteria. Of the seven cases in Group F which were not diagnosed as right ventricular hypertrophy ante mortem by Myers and his associates, Case 37

would have been diagnosed right ventricular hypertrophy according to our criteria. The reliability of our diagnostic criteria when applied to Myers' autopsied cases is demonstrated by the analysis summarized in Table X.

TABLE X. THE FREQUENCY OF VARIOUS ABNORMALITIES OF VOLTAGE OF THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY CALCULATED FROM DATA PUBLISHED ON FORTY AUTOPSIED CASES BY MYERS AND HIS ASSOCIATES,²⁸ AND COMPARED WITH THE PRESENT SERIES OF SIXTY CASES

VOLTAGE OF THE R AND S WAVES	FREQUENCY			
	MYERS ET AL. (40 CASES)		SOKOLOW AND LYON (60 CASES)	
	NO.	PER CENT	NO.	PER CENT
R wave in V_5 or V_6 4.0 mm. or less	18	45	21	35
R wave in V_1 7.0 mm. or more	15	38	35	58
S wave in V_1 less than 2.0 mm.	13	33	30	50
S wave in V_5 or V_6 7.0 mm. or more	13	33	30	50
R wave in V_1 + S wave in V_6 exceeds 10.5 mm.	8	20	26	43
R/S ratio 1.0 or less in V_5 or V_6	11	28	19	32
R wave in aV_R 5.0 mm. or more	9	23	18	30
The ratio $\frac{R/S \text{ wave in } V_5}{R/S \text{ wave in } V_1}$ is less than 0.4	11	28	15	25

CONCLUSION AND SUMMARY

1. An analysis of the electrocardiographic patterns as obtained by unipolar leads in sixty cases of right ventricular hypertrophy is presented and compared with the findings in 150 normal subjects.

2. The typical electrocardiographic pattern of right ventricular hypertrophy, as seen in the tetralogy of Fallot, consists of a tall R wave, a small to absent S wave, and delayed intrinsicoid deflection (delayed ventricular activation time) in the right precordial leads, especially V_1 ; a small R and prominent S wave with a small R/S ratio in the left precordial Leads V_5 and V_6 ; a prominent R wave in aV_R ; the RS-T segment may be depressed and T wave inverted in Lead V_1 or V_2 ; similar RST-T changes may occur in Lead aV_L or aV_F and Leads II and III, but these changes are inconsistent; and the standard leads may show right axis deviation or marked left axis deviation if unusual rotation has occurred.

3. Any of the changes noted in (2) may be absent or less strikingly abnormal when seen in the early development of the pattern of right ventricular hypertrophy. This occurs most typically in cases of mitral stenosis and cor pulmonale.

4. The R/S ratio in Lead V_1 exceeded the maximum normal value of 1.0 in adults in forty-three (72 per cent) of the cases of right ventricular hypertrophy; the R/S ratio in Leads V_5 or V_6 was less than the minimum normal value of 1.0 in nineteen (32 per cent) of the cases of right ventricular hypertrophy. Calculation of these ratios was thus very helpful in the diagnosis of right ventricular hypertrophy.

5. The R/S ratio in Lead V_5 divided by the R/S ratio in V_1 was less than the minimum normal value of 0.4 in fifteen (48 per cent) of the cases of right ventricular hypertrophy in which the ratio could be calculated.

6. The maximum normal height of the R wave of 7.0 mm. in V_1 was exceeded in thirty-five (58 per cent) of the cases of right ventricular hypertrophy.

7. The sum of the total right ventricular potentials (the height of the R wave in Lead V_1 plus the depth of the S wave in Lead V_5 or V_6) in twenty-six of thirty-six cases of right ventricular hypertrophy exceeded the maximum normal value of 10.5 mm. in adults.

8. In chronic cor pulmonale, diagnosed clinically, the only electrocardiographic abnormality may be a small R wave in Lead V_5 or V_6 accompanied by a prominent S wave and a small R/S ratio in these leads. The findings in these leads were similar to those obtained in the same leads in definite right ventricular hypertrophy (as in pulmonary stenosis) and differ from the findings in normal vertical hearts. Such findings, therefore, should permit one to suspect, but not definitely diagnose, right ventricular hypertrophy. In four cases of chronic cor pulmonale in which a small R/S ratio in Leads V_5 and V_6 represented the only abnormal findings, the sum of the R wave in V_1 and the S wave in V_5 exceeded the maximum normal of 10.5 mm. and, therefore, the suspicion of the presence of right ventricular hypertrophy was strengthened.

9. Unipolar precordial leads may differentiate normal from abnormal right axis deviation by demonstrating either the normal pattern or that of right ventricular hypertrophy. The patterns obtained in unipolar precordial leads in cases of normal vertical hearts with right axis deviation of $+80^\circ$ or more do not differ from the findings obtained by similar leads in normal intermediate or horizontal hearts.

10. Unipolar precordial leads in infants were characterized by a greater R/S ratio in Leads V_1 and V_2 than is seen in older individuals; these infants do not, in a limited study, show the delayed intrinsic deflection in Leads V_1 and V_2 or the altered R/S ratio in V_5 and V_6 that characterizes right ventricular hypertrophy.

11. The electrocardiographic position of the heart could not be determined accurately in many cases of right ventricular hypertrophy because neither the right nor left arm leads resembled either the right or left precordial leads. At times the right precordial leads resembled most closely the right arm lead, suggesting that in addition to the clockwise rotation on the longitudinal axis of the heart characteristic of right ventricular hypertrophy, the right ventricle and anterior portion of the cardiac surface is rotated clockwise around the antero-posterior axis of the heart.

Grateful acknowledgment is made to Miss Nancy Gelardi, Mrs. Doris Tuttle, Mrs. Angelina Galente, and Mrs. Suzanne Cahill for their technical assistance, and to Dr. John C. Talbot for statistical advice.

ADDENDUM

To date we have had eighteen cases in which the electrocardiographic diagnosis of right ventricular hypertrophy was made on the basis of the criteria presented. In seventeen patients the right ventricle was at least 5 mm. thick and in the remaining patient a single ventricle 7 mm. thick was presented.

REFERENCES

1. Parkinson, J., and Hoyle, C.: The Heart in Emphysema, *Quart. J. Med.* 6:59, 1937.
2. Rigler, L. G., and Hallock, P.: Chronic Cor Pulmonale, *Am. J. Roentgenol.* 50:453, 1943.
3. Sussman, M. L., Grishman, A., and Steinberg, M. F.: The Roentgenologic Diagnosis of Right-sided Enlargement of the Heart, *New England J. Med.* 228:777, 1943.
4. Schwedel, J. B.: *Clinical Roentgenology of the Heart*, New York, 1946, Paul B. Hoeber, Inc., p. 119.
5. Barnes, A. R., and Whitten, M. B.: Study of T Wave Negativity in Predominant Ventricular Strain, *AM. HEART J.* 5:14, 1929.
6. Berliner, K., and Master, A. M.: Mitral Stenosis, *Arch. Int. Med.* 61:39, 1938.
7. Comeau, W. J., and White, P. D.: The Clinical Significance of Right Axis Deviation in the Electrocardiogram, *AM. HEART J.* 18:334, 1939.
8. Eisenberg, G., and Gibson, S.: Congenital Heart Disease and the Electrocardiogram, *J. Pediat.* 19:452, 1941.
9. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram Including the Cardiac Arrhythmias*, ed. 4, New York, 1941, Paul B. Hoeber, Inc.
10. Katz, L. N.: *Electrocardiography*, ed. 2, Philadelphia, 1946, Lea & Febiger.
11. Hecht, Hans: Brustwandableitungen in der klinischen Elektrokardiographie, *Deutsches Arch. f. klin. Med.* 179:1, 1936.
12. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
13. Sodi-Pallares, C. P.: *Nuevas Bases de Electrocardiografías*, Edición del Instituto Nacional de Cardiología, México, D. F., 1945.
14. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in Chronic Pulmonary Disease, *Am. Rev. Tuberc.* 53:34, 1946.
15. Sokolow, M.: Present Concepts of the Clinical Significance of Unipolar Precordial Electrocardiograms, *California Med.* 65:151, 1946.
16. Goldberger, E.: A Simple, Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar Extremity Leads, *AM. HEART J.* 23:483, 1942.
17. Sokolow, M., and Friedlander, R. D.: The Normal Unipolar Precordial and Limb Lead Electrocardiogram, *AM. HEART J.* In press.
18. Battro, A., and Mendy, J. C.: Precordial Leads in Children, *Arch. Int. Med.* 78:31, 1946.
19. Gubner, R. S., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy, *Arch. Int. Med.* 72:196, 1943.
20. Salazar, M. M., and Sodi-Pallares, D.: Estudio Sobre el Corazon Pulmonar Cronico; Analisis de 14 Casos, *Arch. Int. Cardio. México* 16:22, 1946.
21. Kossmann, C. E., and Johnston, F. D.: Precordial Electrocardiogram. I. The Potential Variations of the Precordium and the Extremities in Normal Subjects, *AM. HEART J.* 10:925, 1935.
22. Sodi-Pallares, D., Paras, O., Cabrera, E., and Mendoza, F.: La Deflexion Intrínseca en Casos Normales y en Hipertrofias Ventriculares, *Arch. Inst. Cardiol. México*, 16:397, 1946.
23. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* 30:162, 1919.
24. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, *AM. HEART J.* 11:163, 1936.
25. Griggs, D. E., Coggin, C. B., and Evans, N.: Right Ventricular Hypertrophy and Congestive Failure in Chronic Pulmonary Disease, *AM. HEART J.* 17:681, 1939.
26. Scott, R. W., and Garvin, C. F.: Cor Pulmonale: Observations in Fifty Autopsy Cases, *AM. HEART J.* 22:56, 1941.
27. Goldberger, E.: *Unipolar Lead Electrocardiography*, Philadelphia, 1947, Lea & Febiger.
28. Myers, G. B., Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, *AM. HEART J.* 35:1, 1948.
29. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, *AM. HEART J.* 34:785, 1947.
30. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, *AM. HEART J.* 37:161, 1949.

Clinical Reports

UNUSUAL FEATURES IN A CASE OF CAROTID SINUS SYNDROME

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SINCE Hering¹ discovered the carotid sinus reflexes and their importance in the nervous regulation of the vascular system, disturbances of the carotid sinus reflexes have become increasingly significant in clinical pathology. The following observation may serve as a contribution to the knowledge of the carotid sinus syndrome.

CASE REPORT

M. D., a 53-year-old man, was readmitted to the hospital for the fifth time in October, 1944, because of attacks of precordial pain, loss of consciousness, and convulsions. At the age of 32 years he fell from a scaffold and fractured the neck of his left femur and several ribs. These injuries were so severe that he was bedridden for two years. He apparently had no intracranial injuries and did not lose consciousness after the fall.

A few months after the accident the patient began to experience attacks of pressure and pain in the precordial region; these usually subsided quickly. During severe attacks, loss of consciousness and convulsions occurred. These symptoms were not present without preceding precordial pain. The frequency of these attacks was quite variable, being absent for periods of one year or recurring many times during one month. Several times during the last few years he was brought to the first aid station of our hospital in an unconscious state.

During the last twelve years the patient suffered, in addition, from attacks of dyspnea accompanied by precordial pain radiating to the left shoulder and arm. At times the patient was persistently dyspneic for periods of days or a week. During these periods severe attacks of asthma, precordial pain, and convulsions were observed. The attacks of precordial pain were independent of excitement, exertion, meals, and cold. The effect of nitroglycerine on the pain and of ephedrine on the dyspnea was inconsistent.

On repeated admissions to the department of internal medicine during the years 1940 to 1944, inclusive, examination revealed the same essential findings. The patient had a plethoric, masklike face and was in good general condition. The pulse was regular at a rate of 80 beats per minute. Between the attacks the blood pressure varied between 125/80 and 155/110. The heart was of normal size and the sounds were of good quality. X-ray films of the heart and electrocardiograms were normal. There were no remarkable findings in the lungs. However, during the periods of dyspnea, expiration was prolonged and dry râles were heard diffusely over both lungs.

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Neurological examination revealed the following pathologic findings: slight nystagmus on fixation, especially when looking to the right side, motor hemiparesis, a slight but distinct central hemihypoesthesia on the left side, and slight hypostereognosis with the left hand. Other disturbances in the nervous system were not found. Urine, blood count and smear, and blood chemistry (urea, sugar, and cholesterol) were normal. On repeated examinations during several admissions the blood Wassermann reaction was negative.

During this present admission it was observed that the typical complete attacks could be produced by pressure on the left carotid sinus region. The slightest pressure was sufficient to produce an attack. No disturbance appeared with pressure on the right side. Palpation of the carotid sinus region on the left and right sides showed no abnormal masses. The spontaneous attacks observed during the patient's stay in the ward were entirely similar to those produced by pressure on the left carotid sinus region.

Phenomena Produced by Pressure on the Left Carotid Sinus as Observed During Admission in 1944.—On slight pressure on the left carotid sinus region, almost instantly the patient experienced a feeling of pressure in the cardiac region and clutched the left chest. At the same time his face assumed an anxious expression and turned red while sweat poured from his forehead and temples. He became short of breath, with difficult and prolonged expiration. At this time wheezing was heard. A few seconds later he became unconscious and convulsions appeared on the right side only. The head was turned to the extreme right and the whole body was turned to the same side. The arms were crossed over his breast. The left leg was bent, while the right leg was stretched out. The pupils were dilated and did not react to light. There was no incontinence of urine, nor was the tongue bitten. There was no Babinski sign. During the attack the pulse was regular and attained a rate of 120 to 140 per minute. Blood pressure readings between the convulsions rose from 125/80 to 180/120. The attacks lasted from a few minutes to one-half hour. An attack could be prolonged at will by the slightest touching of the patient or even of his bed. When the attack was subsiding, slight movement of the bed was sufficient to re-excite turning of the head to the extreme right, stretching of the right leg, bending of the left leg, and then convulsions of the whole body. After the attack, consciousness was regained in a few minutes, but the patient remained confused and dumb for a period varying from one to six hours. With the subsidence of the convulsions the pulse rate and the blood pressure returned to normal and the dyspnea and wheezing disappeared gradually. At times, however, when the patient was in a dyspneic phase, wheezing and prolonged expiration continued for many hours.

Five completely identical attacks were elicited by application of pressure to the left carotid sinus region. Pressure on the right carotid sinus region did not produce attacks. Repeated examination of the blood sugar during the attacks revealed essentially normal values and at no time was hypoglycemia or hyperglycemia observed.

Interrogation of the patient revealed that the attacks came on without his being aware of having applied or having experienced pressure to the neck. It is noteworthy, however, that turning of the head to the extreme right by the physician produced in the patient an unpleasant feeling as though an attack

were imminent. It is also noteworthy that the patient preferred to wear a shirt open at the neck.

The patient refused exploration or even novocainization of the carotid sinus region.

COMMENT

This is a case of carotid sinus syndrome, if we accept as its definition a clinical syndrome which can be elicited by pressure on the carotid sinus region. It is well known that in patients suffering from this disturbance, spontaneous attacks may occur without obvious pressure on the carotid sinus region.

Weiss and Baker² classified the carotid sinus syndrome into three types: (1) syncope accompanied by slowing of the pulse; (2) syncope accompanied by low blood pressure; and (3) syncope with various neurological features, but unaccompanied by bradycardia and hypotension. The case which has been described apparently belongs in the last category. The patient presented some unusual features from the medical and neurological point of view, rarely observed in the carotid sinus syndrome.

The precordial pain, radiating into the shoulder and arm and accompanied by anxiety, was clearly of the anginal type. It is known that in some patients pressure on the carotid sinus may induce an attack of angina pectoris.³ There are two considerations supporting the opinion that in our patient no organic disease of the coronary arteries was present. The first is the fact that after seventeen years of repeated attacks of "angina pectoris" no roentgenologic evidence of cardiac enlargement nor any abnormality in the electrocardiograms was found. The second is that neither exertion, cold, meals, nor excitement induced attacks of precordial pain. It is, therefore, improbable that relative myocardial ischemia was induced by the tachycardia, *per se*, which occurred during the attacks. It has to be assumed that in this case pressure on the carotid sinus led to a spasm of the coronary arteries.

The attacks of dyspnea were clearly caused by bronchospasm. The clinical picture, the absence of cardiac enlargement, and the finding of a normal arm-to-tongue circulation time during a period of dyspnea are evidence against dyspnea of cardiac origin. Respiratory distress and orthopnea have been observed often in carotid sinus syndrome. Attacks of bronchial asthma, however, seem to be unusual. The bronchial spasm existing in this case is different from the deepened and accelerated respiration usually observed as a result of pressure on the carotid sinus in animals.

Although slight acceleration of the pulse rate during attacks of carotid sinus syndrome sometimes has been observed, tachycardia such as that found in the present case seems to be rare. A rise in blood pressure during the attacks of carotid sinus syndrome is also unusual. Danielopolu and associates⁴ distinguished between two types of blood pressure reactions following carotid sinus pressure in man. In most cases they found a reduction of blood pressure; in only a few cases, an increase. It is of interest, in this respect, that, according to Danielopolu,⁵ pressure on the carotid sinus in monkeys always results in

an increase of blood pressure. In healthy subjects Tomanek⁶ observed a slight increase in blood pressure, up to 10 mm.Hg, following carotid sinus pressure. Weiss and Baker² also observed a slight rise in blood pressure after carotid sinus pressure in a few healthy subjects. The highest blood pressure rise found by Mandelstamm and Lifschitz⁷ in healthy subjects as a result of carotid sinus pressure was 30 mm. of mercury. The latter authors, like Weiss and associates,^{2,8} believe that in most cases the stated increase in blood pressure was due to a faulty technique of application of pressure to the carotid sinus region, namely, obstruction of the common carotid artery below the point of its division, leading to a decrease in pressure in the carotid sinus. In our case pressure on the common carotid artery below the region of the carotid sinus had no effect whatsoever. Another explanation of the occurrence of increased blood pressure and also of dyspnea following pressure on the carotid sinus region is the possible induction of anoxemia of the carotid bodies. Some investigators^{9,10} were able to cause severe dyspnea in the dog by obstructing the blood supply to the carotid bodies. The tachycardia observed in our patient, however, seems to invalidate this latter explanation, since in the animal experiment anoxemia of the carotid bodies leads to bradycardia.

In the differential diagnosis a pheochromocytoma has to be considered as accounting for the attacks of tachycardia, hypertension, and sweating. Nuzum and Dalton¹¹ described a case of suprarenal pheochromocytoma in which pressure on the carotid sinus elicited attacks characterized by precordial pressure, sweating, and hypertension, but only slight increase in pulse rate; these were identical with those occurring spontaneously. In our patient no evidence of suprarenal medullary tumor was suggested by x-ray and blood sugar studies. Although the possibility cannot be excluded, the duration of the disease for seventeen years makes the diagnosis of pheochromocytoma improbable.

The neurological syndrome in our patient, consisting of left hemiparesis, hemihypoesthesia, and hypostereognosis was present on the first examination and did not develop further in the following years. It may be assumed that this syndrome developed as the result of the thrombotic occlusion of a blood vessel, occurring during a "carotid sinus" attack. Marmor and Sapirstein¹² observed in a patient the development of left-sided hemiplegia after pressure on the right carotid sinus. At autopsy bilateral thrombosis of the anterior cerebral arteries was found. Askey,¹³ discussing seven cases of transient contralateral hemiplegia occurring after carotid sinus pressure, points out that persistent hemiplegia, developing in the syndrome, is probably due to thromboses or hemorrhages. In our patient, the affected sensibility of the left side points to the involvement of the right artery of the sylvian fissure, the cerebral vascular disturbance, therefore, being localized contralateral to the hypersensitive carotid sinus. The finding of Marmor and Sapirstein¹² of bilateral thrombosis after unilateral carotid sinus pressure makes the assumption of a vascular occlusion contralateral to the hypersensitive carotid sinus in our patient quite possible.

Convulsions are a common feature of the carotid sinus syndrome of the cerebral types. Weiss and Baker² reported the occurrence of generalized tono-

clonic convulsions, as well as unilateral jacksonian attacks. The convulsions in our patient, characterized by turning of the head, the eyes, and the whole body to the right, stretching of the right leg, and bending of the left leg, are of a special type and belong to the group of "frontal epilepsy." Foerster¹⁴ provoked in man typical convulsions by electrical irritation of the frontal lobe. These convulsions consisted in a conjugated turning of the head, the eyes, and the body to the contralateral side with subsequent tonoclonic convulsions in the contralateral extremities. The area where the convulsions originate, called by Foerster "frontal adverse area," is situated in the centrofrontal region and corresponds to Field 6 of Brodmann¹⁵ and Area F B of Von Economo and Koscinas,¹⁶ which is the area agranularis frontalis. This area, because of its agranulated structure, is connected with the gigantopyramidal cortical area rather than with the other frontal types, which have an interior granulated layer. On the basis of the observations of Goldstein and associates¹⁷ and Zingerle,¹⁸ as well as the observations of one of us (L.H.),^{19,20} it has been pointed out that the "frontal" convulsions observed in man correspond clinically in essence to the experimentally produced attack, although with certain variations. In some cases the chief symptom is a forcibly conjugated turning of the head and the eyes to the contralateral side, while the arm and sometimes the leg of the homolateral side are stretched. Finally, there are cases of frontal epilepsy in which both upper extremities take part, the convulsions then having the features of a partial neck reflex. In our patient the convulsions showed the features of a neck reflex, manifesting themselves in the lower extremities by producing stretching out of the leg on the side to which the chin was turned and bending of the other leg. Our observations thus show that in addition to the generalized attack and the unilateral jacksonian attack, the unilateral attack of "frontal" convulsions also can be produced by irritation of a hypersensitive carotid sinus. In our patient pressure on the left carotid sinus produced a contralateral "frontal attack," possibly caused by a reflex anemia of the hemisphere of the same side. Why in one case a generalized attack occurs and in the other a unilateral jacksonian attack or a "frontal" attack is at present not understood.

SUMMARY

A case of carotid sinus syndrome is reported with the unusual medical features of bronchospasm, tachycardia, and increase in blood pressure. From the neurological point of view the contralateral attack of convulsions having the main features of a partial neck reflex and belonging to the type of frontal epilepsy are of interest.

REFERENCES

1. Hering, H. E.: *Die Karotidsinusreflexe auf Herz und Gefaesse*, Dresden and Leipzig, 1927, Theodore Steinkopff.
2. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, *Medicine* 12:297, 1933.
3. Friedman, M.: The Anginal Syndrome as a Manifestation of Hyperactivity of the Carotid Sinus, *AM. HEART J.* 29:37, 1945.

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1. Hering, H. E.: *Die Karotidsinusreflexe auf Herz und Gefaesse*, Dresden and Leipzig, 1927, Theodore Steinkopff.
2. Weiss, S., and Baker, J. P.: *The Carotid Sinus Reflex in Health and Disease*, Medicine 12:297, 1933.
3. Friedman, M.: *The Anginal Syndrome as a Manifestation of Hyperactivity of the Carotid Sinus*, AM. HEART J. 29:37, 1945.

4. Danielopolu, D., Marcu, I., and Proca, G. G.: Sur la mecanisme de production des variations du reflexe sino-carotidien à l'etat pathologique, *Compt. rend. Soc. de biol.* 109:767, 1932.
5. Danielopolu, D., Aslan, A., Marcu, I., Proca, G. G., and Manescu, E.: Les zones reflexogenes carotidiennes, *Presse méd.* 35:1585, 1927.
6. Tomanek, Z.: Carotissinusreflexe Beim Menschen, *Klin. Wchnschr.* 7:898, 1928.
7. Mandelstamm, M., and Lifschitz, S.: Vegetative Herzreflexe, 4 Mitteilung. Die Wirkung der Karotissinusreflexe auf den Blutdruck Beim Menschen, *Wien. Arch. f. inn. Med.* 22:397, 1932.
8. Ferris, E. B., Jr., Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* 14:377, 1935.
9. Winder, C. V., Bernthal, T., and Weeks, W. F.: Reflex Hyperpnea and Vasoconstriction Due to Ischemic Excitation of the Carotid Body, *Am. J. Physiol.* 124:238, 1938.
10. Schmidt, C. R., and Comroe, J. H.: Functions of the Carotid and Aortic Bodies, *Physiol. Rev.* 20:115, 1940.
11. Nuzum, F. R., and Dalton, J. W.: Paroxysmal and Persistent Hypertension in Association With Lesions of Adrenal Glands, *AM. HEART J.* 16:643, 1938.
12. Marmor, J., and Sapirstein, M. R.: Bilateral Thrombosis of Anterior Cerebral Artery Following Stimulation of a Hypersensitive Carotid Sinus, *J. A. M. A.* 117:1089, 1941.
13. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, *AM. HEART J.* 31:131, 1946.
14. Foerster, O.: Die pathogenese des Epileptischen Krampfanfalles: Einleitender Ueberblick, *Klinik und Therapie*, *Deutsche Ztschr. f. Nerven.* 94:3, 1926.
15. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf grund des Zellenbaues, Leipzig, 1909, J. A. Barth.
16. Von Economo, C. F., and Koscinas, G. N.: Die Zytoarchitektonik der Hirnrinde des Erwachsenen Menschen, Berlin, 1925, Julius Springer.
17. Goldstein, K., and Boernstein, W.: Ueber sich in Pseudospontanen Bewegungen Aeuszernde Spasmen und ueber Eigentuemliche Stellungen die "Striaeren" Eerkrankungen. Zugleich ein Beitrag von den Mitbewegungen, den Induzierten Tonusaenderungen und dem Phaenomen der Reflexumkehr, *Deutsche Ztschr. f. Nerven.* 84:234, 1925.
18. Zingerle, H.: Automatosesyndrom beim Linksseitiger Stirnhirnekrankung, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 145:249, 1933.
19. Halpern, L.: Ueber Frontale Epilepsie, *Wien. klin. Wchnschr.* 18:557, 1935.
20. Halpern, L.: Ueber ein Wendungssyndrom des Stirnhirns, *Wien. klin. Wchnschr.* 15:505, 1937.

AURICULAR FLUTTER DURING THE ADMINISTRATION OF CYCLOPROPANE AND CURARE

REPORT OF TWO CASES

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CURARE was first used in anesthesia by Griffith and Johnson,^{1,5} and Cullen³ reported its use in a large number of cases. The alkaloid of curare in use is *d*-tubocurarine, which in therapeutic doses is thought to have no effect upon the electrocardiogram of the normal or diseased heart nor on involuntary or cardiac muscle.⁴ On the other hand, cyclopropane is a very common producer of cardiac arrhythmia; therefore, it was thought advisable to report the following two cases.

CASE 1.—A. E. was a 74-year-old white man who had a negative family history and past history. He had enjoyed good health except that for a number of years he had had attacks of epigastric discomfort, with frequent urination and nocturia. Ten days before admission to the hospital he had severe abdominal pain, with return of the polyuria. Physical examination showed an arcus senilis with arteriovenous nicking and narrowing of the retinal arteries. The only other positive findings were limited to the abdomen, where there was deep tenderness and muscle guarding in the left upper quadrant. The temperature was 100.6° F.; the pulse, 68 per minute and regular; the respirations, 16; and the blood pressure, 110/84. The blood count revealed 3,740,000 red blood cells and 14,300 white blood cells, with 90 per cent polymorphonuclear leucocytes and 10 per cent lymphocytes. The sedimentation rate was 84 mm. in sixty minutes. The urine had a specific gravity of 1.033, 5.0 mg. of albumin, and no sugar. The blood urea nitrogen was 28 mg. and the prothrombin was 92.5 per cent. The Wassermann test was negative. A cyst was discovered in the upper left quadrant of the abdomen, and pyelograms showed it to be on the superior pole of the left kidney and in communication with this organ. An exploratory laparotomy was done and the mass marsupialized. The preanesthesia medication was Pantapone, grain 1/6, and scopolamine, grain 1/200. The anesthesia was Pentothal Sodium and cyclopropane, with the following charted notes: "Pentothal Sodium, 10:55 A.M.; curare, 2.0 c.c., 11:15; curare, 2.0 c.c., 11:25, pulse irregular; curare, 2.0 c.c., 11:45; curare, 2.0 c.c., 11:55; pulse irregular, rate 140, thought to be auricular fibrillation; and at 12:45 P.M. apnea, intercostal paralysis with only diaphragmatic respirations." The electrocardiogram showed auricular flutter with 2:1, 3:1, and 4:1 block, and return to a sinus rhythm with a negative T₂ and T₃ and diphaseic T₄ in five days, after the administration of quinidine sulfate (Fig. 1). The patient made an uneventful recovery.

CASE 2.—E. D., a white married woman, 44 years of age, stated that her mother had died of some type of heart disease, and that she had had growing pains as a child, occasional tonsillitis, with a tonsillectomy at the age of 8 years, and a simple goiter at 11 years of age. At the

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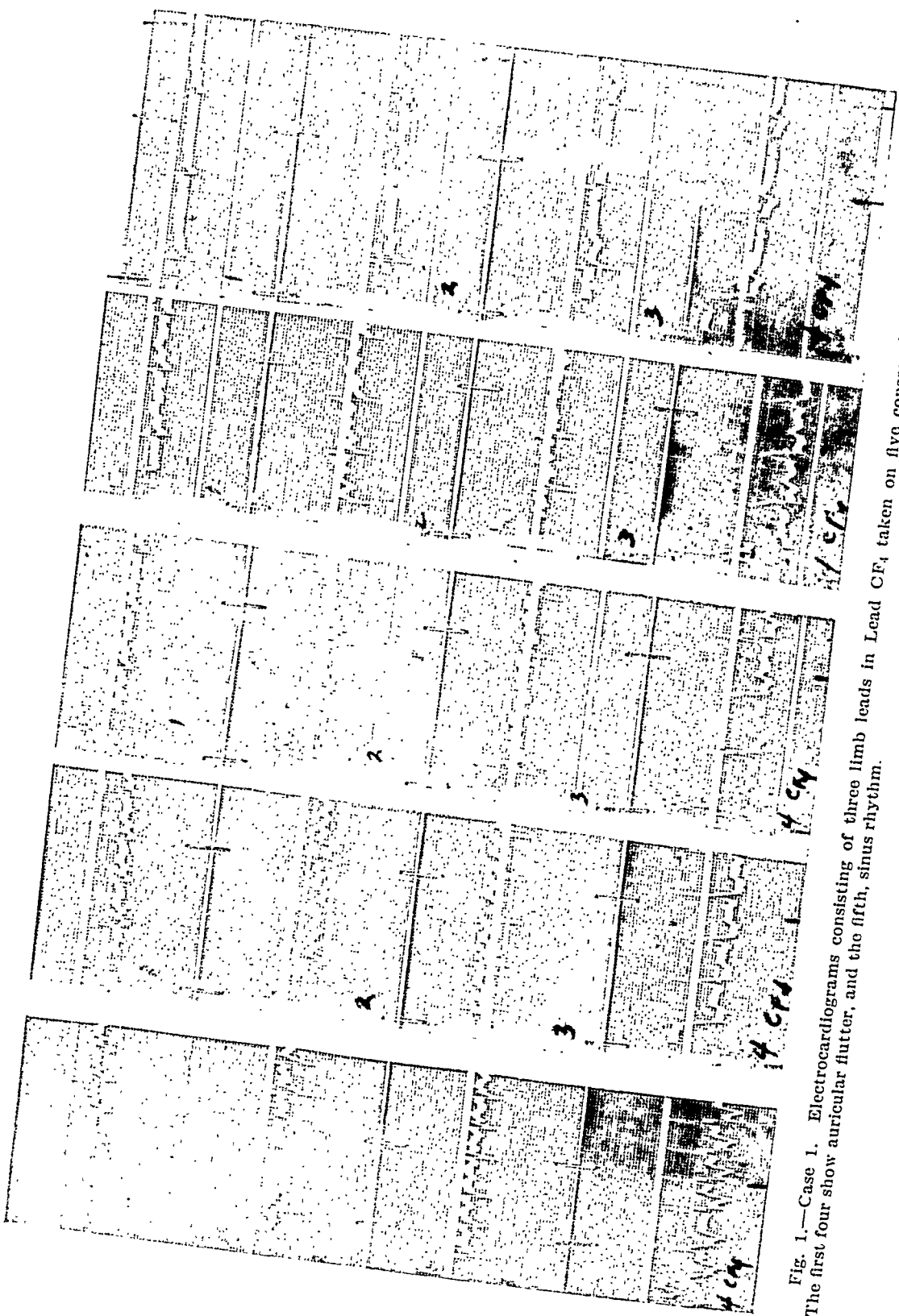


Fig. 1.—Case 1. Electrocardiograms consisting of three limb leads in Lead CF₄ taken on five consecutive days (from left to right). The first four show auricular flutter, and the fifth, sinus rhythm.

age of 12, she began to have palpitation, tachycardia, and flushing on exertion. At the age of 31 years, upon considerable exertion, she became quite nervous, had severe tachycardia, palpitation, occasional slight pain in the lower sternal region, slight dyspnea, and an occasional extrasystole.

A physical examination at the age of 31 years revealed the temperature to be 98.6° F.; the respirations, 16; the pulse rate, 104 per minute and rhythm regular; and the blood pressure, 142/74. There was a thrill, presystolic murmur, booming first sound, and mid-diastolic squeaking sound at the apex, with a systolic murmur at the pulmonic area and along the left border of the sternum. The lungs were clear, the liver was at the costal margin, and there was no edema of the ankles. The orthodiagram showed the left auricular shadow enlarged to the left and posteriorly into the posterior mediastinal space. The anterior transverse diameter was 11.7 centimeters. The electrocardiogram revealed a tendency toward a right axis deviation, and there was a rather pronounced P wave in all leads. The basal metabolic rate was plus 11 per cent, and the Wassermann test and urinalysis were negative. The blood count, sedimentation rate, and blood chemistry were normal, and the vital capacity was 100 per cent of normal. The diagnosis was rheumatic heart disease, with mitral stenosis and insufficiency, and hypertrophy and dilatation. The patient was very comfortable and she improved under the routine and accepted treatment, but the subsequent electrocardiograms showed a slightly lowered T wave in Lead II.

One year later she became pregnant and was delivered at term. Ten days following delivery she had a definite increase in the systolic and drop in the diastolic blood pressure, and a diastolic murmur appeared at the aortic area. After two weeks the signs of aortic insufficiency had disappeared; however, the orthodiagram revealed the transverse diameter as 13.5 cm., and since that time it has remained between 12.0 and 12.5 centimeters. The electrocardiograms had remained unchanged. The patient was symptom free until the age of 44 years, when she noticed a tumor mass in her lower abdomen. The blood pressure was 140/80; the cardiac rhythm was regular, with a rate of 80 beats per minute. The vital capacity was 85 per cent. The hemoglobin was 14.1 Gm.; the red blood cells numbered 4,630,000; and the white blood cells, 6,800, with 73 per cent polymorphonuclear leucocytes and 27 per cent lymphocytes. The nonprotein nitrogen was 24.5 mg. per cent; the urine, negative; and the coagulation time, four and one-half minutes. A hysterectomy was performed for the removal of a uterine fibroid. The anesthesia was Pentothal Sodium and cyclopropane, with the following charted notes: "Pentothal Sodium at 10 A.M.; morphine sulfate, grain, 1/6, atropine sulfate, grain, 1/150, at 11 A.M.; cyclopropane and oxygen at noon; curare (Intocostin) 3.0 c.c. at 12:15 P.M., pulse irregular; rate 110 at 12:20 P.M.; curare 2.0 c.c., pulse irregular, rate 120 at 12:30 P.M.; and at 12:50 P.M. anesthesia was terminated and ephedrine, grain 3/8, was given intravenously." The electrocardiogram showed auricular flutter with 4:1, 3:1, and 2:1 block. The next day the patient was started on 2 cat units of digitalis a day and 15 grains of quinidine sulfate, with an increase of 5 grains a day until the fourth day, when 35 grains of quinidine were given and the auricular flutter disappeared, but the electrocardiogram showed complete heart block. The digitalis and quinidine sulfate were discontinued, and three days later the electrocardiogram showed a normal sinus rhythm with a delay in A-V conduction. However, in one month the tracing was the same as before the operation and anesthesia (Fig. 2).

DISCUSSION

Cardiac irregularities are one of the chief objections to cyclopropane, especially with the higher concentrations of the gas.⁶ Cullen⁷ stated, "We could demonstrate that curare neither increased susceptibility of the heart nor offered protection to the action of cyclopropane." The experiments upon dogs by Perlstein and Weinglass⁸ gave no clear indication as to the exact cause of death in prolonged curarization, but pointed to the heart as the organ principally affected because irregularity or bradycardia was found regularly and the autopsies showed

dilation of the heart. The type of irregularity or bradycardia was not identified and therefore cannot be exactly compared with the disturbance in the two cases reported here: in both cases an irregularity due to auricular flutter, and, in the second case, bradycardia due to complete heart block. These patients received 8.0 and 5.0 c.c. of curare, respectively, which is smaller by comparison than the amounts used in the dog experiments; however, the irregularities occurred immediately after the intravenous injection of only 4.0 and 3.0 c.c. of the drug. Although neither of these patients had a normal heart, one having arteriosclerotic and the other having rheumatic heart disease, they had never had any previous

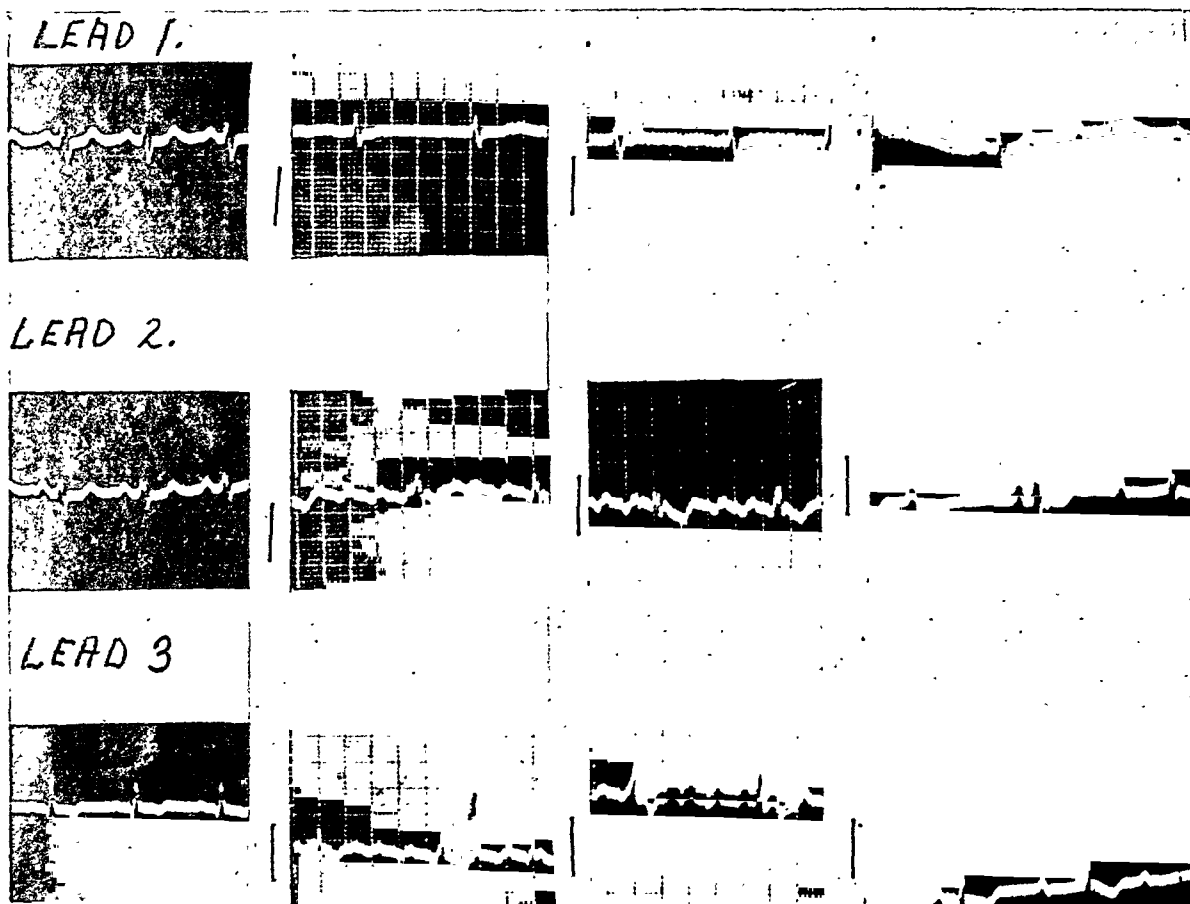


Fig. 2.—Case 2. Electrocardiograms from left to right: a tracing made before curare was given; a tracing taken shortly after injection of curare, showing auricular flutter; a tracing taken one day after injection of curare, showing auricular flutter; a tracing made on the fifth day showing complete heart block. An electrocardiogram made one month later (not illustrated) showed a sinus rhythm with delayed A-V conduction.

irregularity. There did not appear to be any additional heart muscle damage caused by the cyclopropane or curare, because in both cases, when the heart returned to normal sinus rhythm, the electrocardiogram was the same as before the anesthesia. This suggests that the drugs interfered with the normal function of the pacemaker and intrinsic conduction mechanism. Following their experiments, Perlstein and Weinglass concluded that "atropine hastens the lethal effect

of curare," and showed that rapid death occurred in atropinized dogs after curarization, and immediate death, in two dogs, after the injection of a physiologic dose of atropine. The two cases herein reported gave no information relative to the action of atropine and curare because the first received scopolamine, grain 1/200, and the second received atropine, grain 1/150.

CONCLUSION

Two cases of auricular flutter following the use of curare during cyclopropane anesthesia are reported.

REFERENCES

1. Griffith, H. R., and Johnson, G. E.: Use of Curare in General Anesthesia, *Anesthesiology* 3:418, 1942.
2. Baird, J. W., and Adams, R. C.: Curare in General Surgery, *Proc. Staff Meet., Mayo Clin.* 19:200, 1944.
3. Cullen, S. C.: Use of Curare for Improvement of Abdominal Muscle Relaxation During Inhalation Anesthesia, *Surgery* 14:261, 1943.
4. Ruskin, A., Ewalt, J., and Decherd, G.: Electrocardiogram of Curarized Human Patients, *Dis. Nerv. System* 4:335, 1943.
5. Griffith, H. R.: The Use of Curare in Anesthesia and Other Clinical Purposes, *Canad. M. A. J.* 50:144, 1944.
6. Knight, R. T., and Baird, J. W.: Anesthesia for the Ageing and Aged, *Lancet* 64:183, 1944.
7. Cullen, S. C.: Clinical and Laboratory Observations on the Use of Curare During Inhalation Anesthesia, *Anesthesiology* 5:166, 1944.
8. Perlstein, M. A., and Weinglass, A.: Fatal Effects of Prolonged Complete Curarization, *Am. J. Dis. Child.* 67:360, 1944.

Abstracts and Reviews

Selected Abstracts

Myers, J. D., and Hickam, J. B.: An Estimation of the Hepatic Blood Flow and Splanchnic Oxygen Consumption in Heart Failure. J. Clin. Investigation 27:620 (Sept.), 1948.

Thirteen patients with congestive heart failure, associated with a reduced cardiac output and increased blood volume, were studied by the hepatic vein catheterization technique. Liver blood flow was determined by the bromsulphalein method.

In cardiac failure the liver gets its usual percentage (20 to 24 per cent) of the reduced total cardiac output, and thus differs from the kidney, which suffers a disproportionate reduction in blood flow. There is a compensatory increase in hepatic arteriovenous oxygen difference, which under rest and fasting conditions maintains a normal splanchnic oxygen difference. There is a poor correlation between the level of hepatic blood flow and right atrial or peripheral venous pressure.

WAIFE.

Nelson, H. G., and the Personnel of United States Naval Medical Research Unit 4: Studies on Rheumatic Fever: Observations on Tonsillar Carriers of Hemolytic Streptococci; The Effect of Tonsillectomy and the Administration of Penicillin on Rheumatic and Nonrheumatic Fever Patients. J. Infect. Dis. 83:138 (Sept.-Oct.), 1948.

A study was made of the comparative incidence of Group A hemolytic streptococci obtained from cultures of the throats and excised tonsils of rheumatic and nonrheumatic fever patients who had been selected for tonsillectomy. Of the seventy-five rheumatic fever patients, twenty-two were considered to have a low-grade activity of the disease and fifty-three showed no evidence of activity for at least one month prior to operation. There were sixty-four nonrheumatic patients.

Routine throat cultures prior to operation were positive for Group A hemolytic streptococci in only 2.7 per cent of the rheumatic fever patients. Positive throat cultures for Group A hemolytic streptococci were similarly found in 3.1 per cent of the nonrheumatic patients prior to tonsillectomy. Group A streptococci were found in the excised tonsillar tissue of 33.3 per cent of the rheumatic fever patients. There was no significant difference in the percentage of positive cultures recovered from patients with continuing activity, as compared with those in the inactive group. Positive cultures were obtained from the tonsils of 15.6 per cent of the nonrheumatic fever patients.

Penicillin was given preoperatively to patients whose cultures yielded hemolytic streptococci. Postoperative penicillin therapy was given to all patients. The twenty-two patients with low-grade activity showed no increase in activity following tonsillectomy, and all but two of this group became inactive within three months. Of the group of fifty-three patients who had been considered inactive at the time of tonsillectomy, ten had minor manifestations of activity following operation, but all became inactive at the end of two months.

The authors conclude that low-grade activity of rheumatic fever does not contraindicate tonsillectomy when combined with postoperative penicillin therapy, and that cultures from excised tonsils appear to give more accurate information as to the actual incidence of streptococcal carriers than do routine throat cultures.

SCHWARTZ.

Gold, H., Modell, W., Kwit, N. J., Shane, S. J., Dayrit, C., Kramer, M. L., Zahm, W., and Otto, H. L.: Comparison of Ouabain With Strophanthidin-3-Acetate by Intravenous Injection in Man. *J. Pharmacol. & Exper. Therap.* 94:39 (Sept.), 1948.

One milligram of strophanthidin-3-acetate (one of the synthetic esters of strophanthidin) and 0.5 mg. ouabain were diluted to 10 c.c. and administered intravenously to patients with auricular fibrillation and clinical evidence of congestive heart failure. Each patient was given both drugs at different times so that individual variations in response could be controlled. None of the eight patients studied had received any digitalis compounds for at least three weeks prior to the test. Slowing of the ventricular rate was used as an objective sign of digitalization.

Both drugs showed rapid effects. With strophanthidin-3-acetate, 70 per cent of the maximum ventricular slowing was seen within five minutes and the maximum slowing occurred within ten minutes. The ventricular rate returned to its preinjection level in four hours or less. With ouabain, 50 per cent of the maximum slowing was evident within ten minutes and the maximum effect occurred within one to two hours. The ventricular rate did not return to its preinjection level for thirty-six hours. No toxic effects were noted with either drug. There was improvement in the clinical picture coincident with the slowing of the ventricular rate.

The transitory, extremely rapid, and moderately short duration of action of strophanthidin-3-acetate suggests that it might be of therapeutic value in acute cardiac emergencies, such as paroxysmal pulmonary edema, and in some of the paroxysmal tachycardias. Its relatively short duration of action would decrease the danger of prolonged toxic reactions in patients receiving digitalis compounds.

GODFREY.

Donovan, G. E.: Modern Phonocardiography. *Lancet* 6524:401 (Sept. 11), 1948.

The modern practice is to record the heart sounds linearly, stethoscopically, or logarithmically. The author describes a *phono-electrocardioscope* which permits the direct, instantaneous, simultaneous, and constant viewing of a pair of cardiac phenomena such as the phonocardiogram and electrocardiogram. The phonocardiogram represents amplified heart sounds recorded logarithmically. The instrument consists of a double-channel electronic valve amplifying unit with frequency control, intensity control, tone-compensated volume control, a double-beam cathode ray oscilloscope, and a long-persistent fluorescent screen. If permanent records are desired, photographs can be taken of one traverse of the cathode-ray spots on the screen. Several still photographs of the fluorescent screen are demonstrated as examples.

The author suggests that many of the inaudible vibrations which can be recorded (such as the four components to the first and second heart sounds) may eventually prove to have almost as much clinical significance as have the cardiac sounds and murmurs.

WAGNER.

Wolff, G.: Childhood Mortality From Rheumatic Fever and Heart Diseases. *Child. Bureau Pub.* 322, Washington, D. C., 1948.

In a statistical study of death rates in the United States during the years 1939 to 1941, it was found that at least 12,000 deaths were caused by acute rheumatic fever and its sequelae in childhood. Among the nonwhite children with ages ranging from 5 to 19 years, there were 16.6 deaths reported per 100,000 population; among white children the death rate was 11.1 per 100,000. With increasing age in both sexes and racial groups, there was a distinct increase in the death rate for rheumatic heart disease.

The nonwhite group consistently had a higher mortality rate than the white group. This suggests that adverse social and economic conditions are important factors. When analyzed by geographic divisions, these race differences were most significant in the Middle Atlantic States, but in the Mountain State division, higher death rates were observed for white children, as compared with nonwhite children.

No consistent sex differences in mortality rates were seen, except in the group between the ages of 15 to 19 years. In this age group the nonwhite females showed a distinctly higher rate than nonwhite males, while in the white group the rate for females was lower than for males.

In general, the mortality rate is highest in the Middle Atlantic States and lowest in the Pacific Coast States. In the Mountain Division, the rate was exceptionally high for the white children in all age groups.

The range of the crude rate for mortality from acute rheumatic fever plus diseases of the heart ranged from 5.3 in Vermont to 22.4 in Utah; the average for the United States was 11.7 per 100,000.

WAIFE.

Luisada, A., and Fleischner, F. G.: Studies of Fluorocardiography: Tracings of the Left Ventricle in Myocardial Infarction. *Acta cardiol.* 308 (No. 4), 1948.

Twenty patients with old or recent myocardial infarctions were studied by means of fluorocardiography. The graphic study was made in the posteroanterior position and in both anterior oblique positions.

Several abnormalities of ventricular systole and diastole were recognized. Among these, lack of pulsation and inverted pulsation (paradoxical pulsation) in a circumscribed area were considered as the most significant findings, the former, pointing to an area of "local paralysis"; the latter, to a "dynamic aneurysm" of the ventricular wall. Evaluations of the dynamic results of such abnormalities are given. The reasons for suggesting the two new terms are discussed.

Correlation of the findings with electrocardiographic data revealed a coincidence of about 90 per cent. In general, the area presenting an abnormality of contraction was found to be more extensive than indicated by the electrocardiogram.

The findings confirm those of previous roentgenkymographic studies. The reasons for a greater exactitude and broader applicability of fluorocardiography in comparison with roentgenkymography are given.

AUTHORS.

Bechgaard, P.: Paroxysmal Ventricular Fibrillation With Recovery. *Acta med. Scandinav.* 132:9 (No. 1), 1948.

Twenty-five cases with electrocardiograms showing transient ventricular fibrillation are cited from the literature. All of the patients had severe heart disease, usually with A-V dissociation. All but three died shortly after the fibrillation was recorded. Two patients were able to return to work and the author adds the report of a third instance.

A 50-year-old man with a history of rheumatic fever at the age of 28 had fainting fits for several years, then a six-months' remission, following which he developed nocturnal palpitation and spells of dyspnea with a decreased diurnal exercise tolerance. He then had several fits consisting of sudden disappearance of the pulse, cyanosis, focal convulsions, and hyperpnea, with the return of an irregular pulse which then became regular. An electrocardiogram was normal five days before the attacks, with a P-Q interval of 0.20 second. During two attacks, however, ventricular fibrillation was recorded and in a third the entire electrocardiograph sequence of (1) ventricular flutter-fibrillation for 125 seconds, (2) asystole for 1.4 seconds, (3) A-V dissociation with variable ventricular complexes and an auricular rate of 100 per minute, (4) a prolonged P-Q interval, and (5) a normal tracing six minutes after the attack.

Strophanthus, 0.25 mg., was given twice at four-hour intervals with cessation of the attacks during one night. Three attacks occurred the next morning but with another 0.50 mg. of strophanthus, together with digitalis for more prolonged action, no more attacks occurred. There were no evidences of a cardiac lesion aside from the arrhythmia. The patient was able to return to work and an electrocardiogram was normal six months after discharge. He had only one questionable attack in the thirteen months following hospitalization but dropped dead at the end of this period.

Necropsy showed slight, nonstenosing coronary atheroma and a heart which weighed 330 grams, but no other abnormalities, gross or microscopic. The cause of the disturbance of rhythm was therefore unknown.

SAYEN.

Eckerstrom, A.: Libman-Sacks Syndrome. *Acta med. Scandinav.* 132:21 (No. 1), 1948.

The author presents the case history of a 45-year-old woman who had had bone tuberculosis and Graves' disease with a thyroidectomy in the past but who was in good health for five years preceding the development of joint pains and stiffness followed by fever, acrocyanosis, digital pea-sized spots of purple color, butterfly cyanosis of the face, and retinal perivascular lesions. Studies revealed anemia and hyperglobulinemia. The sedimentation rate was 120 mm. per hour at room temperature and 31 mm. per hour in a refrigerator. The increased protein was mainly a gamma globulin which migrated on electrophoresis somewhat more rapidly than the normal gamma fraction does. The albumin-globulin ratio became 1:2. Death occurred after eight months, having been preceded by increased erythema of the cutaneous lesion, higher fever, and signs of polyserositis. At autopsy there was a pericardial effusion, a small amount of ascites, a swollen, fatty liver, and slight splenomegaly. Histologic study revealed increased myocardial, splenic, and lymphatic connective tissue, with vascular fibrinoid changes especially in the pre-capillaries. The glomeruli were swollen and infiltrated with cells. No endocarditis was present and the heart valves were not described. The clinical and microscopic picture is considered to be that of Libman-Sacks disease. The importance of suspecting such a condition in the presence of hyperglobulinemia, fever, arthritis, and polyserositis is stressed.

SÄVEN.

Lazarus, S., Munro, H. N., and Bell, G. H.: Capillary Strength Tests in Scurvy and Their Reactions to Vitamin C and Vitamin P Therapy. *Clin. Sc.* 7:175 (No. 2), 1948.

These authors used the positive pressure tests of Göthlin and the negative pressure tests of Scarborough in three groups of patients who were studied for capillary fragility. One comprised fifteen patients with scurvy (mean age, 62 years). Subcutaneous hemorrhages and petechiae were found in all of this group. Plasma levels of ascorbic acid and ascorbic acid saturation tests were compatible with the diagnosis of scurvy. The second group comprised twenty-nine male patients (mean age, 74) who served as in-patient controls. The third group consisted of twenty healthy hospital visitors of approximately the same age. The patients with scurvy were placed on a diet free of vitamin C and vitamin P and measurements of capillary strength were made before treatment and at weekly intervals thereafter.

Although the mean number of petechiae obtained by the positive pressure test was greater in the scorbutic than in the nonscorbutic patients, the overlap was so great that it was not considered of diagnostic value. After large doses of ascorbic acid (an average of 9.6 Gm. over a twenty-day period), the signs and symptoms of scurvy cleared up completely in every case; but in the group as a whole the mean petechial readings obtained with both positive and negative pressure tests were unchanged by the administration of ascorbic acid.

Several preparations said to have vitamin P activity were given to scorbutic patients with and without previous treatment with ascorbic acid. No alteration in the capillary strength as measured by the positive pressure test was noted. There was a slight increase in the capillary strength in one skin area as judged by the negative pressure test.

It would appear that the poor correlation between the positive and negative pressure test in individual cases can be explained only in that they measure quite different properties. The authors conclude that these tests of capillary strength do not measure the fundamental vascular lesion in scurvy. They suggest that scurvy is more likely to develop in subjects who already have some form of capillary weakness, that is, that individuals with weak capillaries develop scurvy after a smaller deficiency of vitamin C than do those with strong capillaries.

WAIFE.

Berg, W., Delius, L., and Schildge, E.: Hypnosis and Venous Pressure. *Ztschr. f. Kreislaufforsch.* 37:691, 1948.

Induced emotional upsets and suggested exercises during hypnosis resulted in an appreciable rise of venous pressures in six subjects. This was largely independent of arterial pressures, respiration, muscular contraction, and intramuscular pressures.

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during the hospital course and showed no significant changes in the QRS complexes of either the precordial or limb leads and no changes in the T waves other than those attributable to digitalis. For this reason, the lesion was considered to be old and healed. For further localizing evidence, additional leads were obtained from points at the intersections of a horizontal line at the level of the junction of the third intercostal space and sternum with vertical lines through precordial Positions 4, 5, and 6. The tracing taken at the level of the third intercostal space in the mid-clavicular line closely resembled Lead V_4 , and that taken high in the midaxillary line was almost identical with Lead V_6 . However, the record from the anterior axillary line at the level of the third intercostal space was characterized by an abnormal QR complex and dome-shaped RS-T segment. This finding, when compared with the customary Lead V_6 and with other records taken at the same horizontal level, was diagnostic of a localized high lateral infarction.

Pathologic Findings.—The heart weighed 749 grams because of left ventricular hypertrophy. A patchy healed infarct which involved the subendocardial one-half of the lateral wall, as outlined in Fig. 9, was found grossly and confirmed microscopically. The extension into the posterolateral wall of the apex was not evident in Lead aV_F , but might have constituted an indirect factor in the relatively high R waves in Leads V_2 and V_3 . The infarction of the basilar portion of the lateral wall adequately accounted for the QR pattern in aV_L and in the lead high in the anterior axillary line, whereas the absence of infarction of the anterolateral aspect of the apex could explain the lack of a diagnostic pattern in Leads V_4 , V_5 , and V_6 . This case illustrates well the value of supplementary high precordial leads in the diagnosis of infarcts situated high in the lateral wall of the left ventricle.

CASE 146.—A 72-year-old man had had classical angina pectoris for two years. On June 1, 1945, he was seized with a much more severe attack of retrosternal constriction followed by syncope. He was brought to the hospital in shock one hour later and remained in profound circulatory collapse until his death thirty-nine hours after admission.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 10 were obtained on June 1, two hours after the onset of the pain and before the administration of cardiac glycosides, and on June 2, twenty-two and one-half hours later, after the administration of 1.6 mg. of Cedilanid. In the record of June 1, there was a marked sinus bradycardia (36 per minute) with occasional escaped nodal beats. The initial phase of the QRS complex was upright and normal in contour in all precordial leads. The striking feature of the first five precordial leads was the marked depression of the RS-T junction, the exceptionally broad U-shaped T wave, which caused moderate prolongation of the Q-T interval. The administration of quinidine and allied drugs could be excluded positively. Two possible causes for the RS-T depression remained for serious consideration: (1) a reciprocal manifestation of a recent posterolateral infarct; and (2) a direct result of acute ischemia or early infarction of the subendocardial portion of the anterolateral wall of the left ventricle and the adjoining left side of the septum. The slight elevation of the RS-T junction in Leads V_6 and aV_F raised the question of recent posterolateral infarction. The absence of a Q wave from these leads and the contour of the RS-T segment and T wave were against posterolateral infarction, but did not exclude it, because of the short interval between the onset of symptoms and the recording of the electrocardiogram. Nevertheless, a diagnosis of acute ischemia or very early infarction of the subendocardial portion of the anterolateral wall of the left ventricle and left side of the septum was favored in the ante-mortem interpretation because the downward displacement of the RS-T segment in the first five precordial leads greatly exceeded the upward displacement in V_6 and aV_F . Lead aV_L showed an M-shaped QRS complex of very low voltage and an inverted T wave, which were probably transmitted from the transitional zone as a result of semivertical position of the heart. In the next tracing there was no significant change in the QRS pattern in the standard leads or in aV_R , aV_L , V_1 , and V_2 . The initial phase of the QRS complex was still upright in the four remaining precordial leads, but was reduced to approximately one-third of its former voltage. The marked decrease in the amplitude of the R wave in these leads was suggestive of patchy infarction of the anterolateral wall of the left ventricle. Close scrutiny of Lead aV_F disclosed the appearance of a minute Q wave 0.5 mm. in depth without significant change in the upright deflection. Although this Q wave was too small to be of diagnostic significance, the parallelism of the T-wave evolution to that of Lead V_6 suggested that the lesion

The mass was injected at a pressure from 50 to 100 mm. of mercury. The radiopaque mass issued from the renal vein and was collected in a test tube; in every instance, glass beads were recovered from this perfusate.

This mixture was injected into sixteen isolated human kidneys with intact capsules. Beads 90 to 440 microns in diameter were recovered from the renal vein in ten of the sixteen kidneys; the maximum diameters were 200 microns or more. Neither age nor disease played a role in determining the size of the beads recovered. The same results were obtained when decapsulated kidneys were used.

The authors conclude that these observations indicate the presence of direct arteriovenous communications which must by-pass the capillary bed in the normal human kidney since these spheres were too large to pass through the capillaries.

This experiment was repeated in living rabbits and dogs under ether anesthesia, using a saline suspension of beads and using the lungs as the trap for the beads instead of cannulizing the renal vein. Beads ranging in size from 50 to 180 microns were recovered from the lungs of the rabbits. In seven animals the kidneys were intact and in seven the kidneys were decapsulated. The results indicate the presence of arteriovenous shunts in the kidneys of living rabbits and dogs.

The authors finally conclude that if the concept of a functional extraglomerular circulation in the normal kidney is accepted, based upon their experiments, a re-evaluation of the dynamics of renal flow of the blood is in order.

BERNSTEIN.

Kallner, S.: Thrombosis as a Complication of Internal Diseases. Arch. Int. Med. 81:126 (Feb.), 1948.

The author studied patients with pneumonia in whom fever persisted after the pneumonia had been apparently controlled by antibiotic therapy. The author used heparin and Dicumarol to treat the thrombosis, which he feels causes the fever to persist and which he thinks is located in the venous system either of the pelvis or of the lower extremities. With this therapy he gives massage to the lower extremities and permits early movement of the lower extremities and trunk. Therapy is continued until the patient is out of bed and moving about freely. The same technique is used for suspected thrombotic complications in the treatment of cases of heart disease, anemia, parturition, and elderly patients who have been confined to bed for a long time for any reason and in any cases in which a manifest thrombosis has been present.

He states that though he has used anticoagulants in the treatment of cardiac infarctions, it is too early to make any statements regarding the results. Heparin was also used in a case of transfusion reaction in which there was anuria. Two hours after the start of heparin therapy the anuria cleared up and long fibrin casts of tubuli were voided.

Finally, in fibrinous bronchitis heparin was used to decrease or counteract the deposit of fibrin, and, when combined with ephedrine and epinephrine, is characterized by the author as "life saving."

BERNSTEIN.

Thomas, S. F., Alto, P., and Garland, L. H.: Roentgen Cardiac Kymography: Electrocardiographic Correlation. California Med. 68:126 (March), 1948.

The purpose of this paper is to re-evaluate the roentgen cardiac kymograph and to demonstrate that the kymogram sometimes gives information which is not obtainable by any other means.

Routinely, exposures of 1.5 to 2 seconds were made in mid-inspiration with the patient as relaxed as possible in order to avoid a Valsalva or Müller effect. Films in forced inspiration and expiration were made on occasion to confirm or rule out certain minimal findings. The criteria for kymographic diagnosis were the depth (or height), shape, and phase of the waves. The authors found that in most of the patients in this series the waves were usually under 4 mm. in depth. However, in the patients with myocardial disease of any type, the height (or depth) of the waves was often 2 mm. and frequently less than 1 millimeter. Other findings sometimes suggestive of disease of the myocardium were "peaking" of the waves where the waves come to an abrupt point. Splintering of the waves (both systolic and diastolic) was regarded as important

in the diagnosis of disease, especially when it was accompanied by waves of low amplitude which appeared fuzzy (unsharp). The suppression of waves or absence of movement, or the outright reversal of movement, in any area was considered diagnostic of myocardial damage, and when this occurred in the presence of suitable associated findings, an area of infarction was diagnosed. Localized adhesive pericarditis may produce suppressed and fuzzy waves and mimic an area of localized myocardial damage, but the condition was not encountered in this series. The term myocardial damage is used in this report to include various cardiac abnormalities from myocarditis through myofibrosis to frank infarction.

Over 350 sets of kymograms were made. The authors used the electrocardiogram as an accepted test for the diagnosis of major cardiac disease and then matched the kymogram against this method. The two methods correlated in 80.5 per cent of the cases, or 201 patients. Properly interpreted, roentgen kymograms have been demonstrated as a reliable source of additional information and in a small percentage of cases can provide information not obtainable clinically or even by electrocardiogram.

Illustrative cases are used to bring out the various points of interest.

BELLET.

Rodriguez, R., and Root, H. F.: Capillary Fragility and Diabetic Retinitis. New England J. Med. 238:391 (March 18), 1948.

This report is concerned with the results of the Göthlin positive-pressure test for determining the capillary fragility in diabetic patients. The findings reported deal with three groups of patients: nonselected diabetic patients; diabetic patients with varying degrees of retinopathy; and patients with diabetic retinitis or retinitis proliferans and high degrees of capillary fragility, who were treated with rutin.

The capillary fragility was found to be increased in forty patients (40 per cent), borderline in four (four per cent), and normal in the remaining fifty-six (56 per cent). Diabetic retinitis and hypertension were the most closely related abnormalities among the forty patients with increased capillary fragility. Twelve of these forty patients with increased petechial counts had retinitis with hypertension and fourteen had retinitis with normal blood pressure. In the group of eight patients with retinitis proliferans the blood pressure was normal in two and above 150/90 in the remaining six. In the entire group, the incidence of poor capillary resistance with hypertension was 27.5 per cent. Among the forty patients with abnormal capillary fragility, normal blood pressure and normal fundi were found in three (7.5 per cent). This group confirms the judgment that increased capillary fragility may be present in young persons with diabetes of long duration as one of the earliest signs of arteriosclerosis, which will subsequently be manifest in nephritis, hypertension, and general arteriosclerosis. Among the fifty-six diabetic patients of the nonselected group who had normal capillary fragility, the fundi were normal in fifty-four and retinal damage was present in only two. From the authors' observations it seems clear that diabetic retinopathy seldom occurs in patients who do not have some degree of increased fragility of the capillary walls.

The authors studied an additional group of fifty-six patients with diabetic retinopathy. The petechial index was increased in forty-seven (83.9 per cent) and borderline in nine (16.1 per cent); no patient was found to be normal.

BELLET.

Bronstein, J.: The P Wave in Precordial Leads in Chronic Bronchopulmonary Disease. Rev. argent. de cardiol. 15:105 (March), 1948.

No significant abnormalities in the P wave of precordial leads in fifty patients with bronchopulmonary disease of varying severity were noted in a large number of precordial leads taken from the vicinity of the sternum and to the right and left of it. In thirty-five of these subjects a definite P pulmonale was present in standard bipolar limb leads.

HECHT.

Etala, F., and Berreta, J. A.: A Clinical and Anatomical Study of the Post-tachycardic Syndrome. *Rev. argent. de cardiol.* 15:133 (March), 1948.

A 20-year-old patient had suffered from repeated attacks of paroxysmal dyspnea and was admitted to the hospital during an attack of tachycardia of ventricular origin which had resulted in congestive failure. Following the administration of 4.0 Gm. of quinidine intravenously over a four-day period the normal sinus rhythm was re-established, but the patient exhibited severe toxic reactions including convulsive seizures. The patient recovered. Two years later a similar episode occurred which was controlled by 1.0 Gm. of quinidine given intravenously, but the patient died shortly thereafter in profound shock. Serial electrocardiograms obtained during the first episode revealed sharp inversion of the terminal portion of the T wave in Lead I similar to that observed in anterior myocardial infarction. It reverted to a normal pattern before discharge. On the second occasion inversion of the T wave occurred in all three standard limb leads and in Leads V_4 , V_5 , and V_6 . Although profound myocardial depression may be considered to have been the cause of death, no abnormal pathologic findings were demonstrated at autopsy.

HECHT.

Friedman, S. M., Friedman, C. L., and Polley, J. R.: Potentiation of the Hypertensive Effects of Desoxycorticosterone Acetate (DCA) by Various Sodium Salts. *Am. J. Physiol.* 153:226 (May), 1948.

A hypertensive syndrome was produced in rats by the administration of DCA ("hormonal" hypertension). The blood pressure raising effect of the DCA was intensified when organic and inorganic sodium salts were added to the drinking water of the animal, and this seemed to be dependent on the excess intake of the sodium ion. The phosphate ions were found to be damaging to the kidney even in the absence of DCA.

The degree of blood pressure elevation did not parallel the degree of renal damage, but the electrolyte disturbances (depression of potassium and chlorides) seemed to follow impairment of renal function.

Elevation of blood pressure consistently preceded impairment of renal function, but renal hypertrophy was always present when renal function was unimpaired following DCA administration. The authors assume, therefore, that DCA causes an initial intrarenal derangement which may be the cause for the resultant hypertensive syndrome.

HECHT.

Hamilton, W. F., and Remington, J. W.: Some Factors in the Regulation of the Stroke Volume. *Am. J. Physiol.* 153:287 (May), 1948.

The authors calculated the stroke volume of the heart from the pressure pulse contour of intact dogs. They recognize three mechanisms which regulate stroke volume.

1. *Change in Peripheral Resistance.*—Acute increases of aortic pressure decrease stroke volume and external cardiac work. Decrease of aortic pressure increases these values. The changes represent mechanical effects in the face of unchanged contractile powers of the heart.

2. *Change in Diastolic Size.*—When induced by acute increases in peripheral resistance, changes in the diastolic size of the heart occur which tend to increase stroke volume. These are rarely sufficient to balance or to overcome the effects listed under (1) even when the pericardium is removed.

3. *Sympathetic and Sympathomimetic Stimulation of Cardiac Muscle.*—If peripheral resistance is not greatly altered, sympathetic stimulation increases the contractile power of the heart and raises stroke volume and external cardiac work.

In these experiments changes in resistance to ejection and myocardial stimulation are more important in regulating stroke volume than changes in diastolic filling pressures.

HECHT.

Hamilton, W. F., Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Jr., Wheeler, N. C., and Witham, A. C.: Comparison of the Fick and Dye Injection Methods of Measuring the Cardiac Output in Man. *Am. J. Physiol.* 153:309 (May), 1948.

Two sets of data are being reported: both employ almost simultaneously the dye injection method for estimating cardiac output and the catheterization procedure. In eighteen patients studied in Georgia, oxygen consumption for the Fick formula was obtained through a basal metabolism machine and sampling of the dyed arterial sample was accomplished by a rotating kymograph drum. Mixed blood was obtained from the auricles or ventricles. In the thirty patients studied in New York, samples were obtained from the pulmonary artery or right ventricular outflow tract and dyed arterial samples by means of an escapement mechanism drum. The dyed samples were read with a Beckman spectrophotometer at 625 and corrected for turbidity and hemolysis by readings at 725 and 540, respectively.

In forty-eight determinations on thirty-one subjects the results agreed within 25 per cent in all but six subjects. Scatter was equal so that the means of all determinations were almost identical.

HECHT.

Moore, J. C., Schadle, O. W., and Lawson, H. C.: Measurement of the Circulating Red Cell Volume With Methemoglobin-Tagged Cells. *Am. J. Physiol.* 153:322 (May), 1948.

After a suspension of red blood cells containing large amounts of methemoglobin was injected into splenectomized, anesthetized dogs, the circulating red cell volume was calculated from the methemoglobin content of the arterial blood. The values obtained by this method corresponded well with the data obtained from the increase in the volume of packed red cells resulting from the injection of the cell suspension, and the decrease in the hematocrit readings resulting from plasma infusions. The use of methemoglobin-tagged cells produced values consistently lower than those obtained from the usual dye-injection (T-1824) method of determining plasma volume.

Repeated measurements with the methemoglobin method following an increase in the red cell mass produced by the injection of cells or a decrease in cells following hemorrhage gave results which were in close agreement with expected values.

HECHT.

Shipley, R. E., and Helmer, O. M.: Observations on the "Sustained Pressor Principle" in Different Animal Species. *Am. J. Physiol.* 153:341 (May), 1948.

Further studies have been made on the sustained pressor principle (SP), a pressor substance found in the plasma of cats during prolonged hypotension. SP is apparently produced by the kidneys during the hypotensive phase. Unlike other pressor agents, SP causes a sustained elevation of blood pressure for several hours when it is injected intravenously into recently nephrectomized cats. In these studies SP could be demonstrated in the plasma of rats and dogs subjected to hypotension by bleeding, and in whole blood obtained post mortem from patients dying after a prolonged period of hypotension.

Nephrectomized dogs, cats, and rats were found to react with sustained pressure elevations to the injections of plasma containing the SP.

After the intravenous injection of semicrude kidney extracts from various species (the horse, sheep, hog, cat, dog, rat, and rabbit) into nephrectomized cats, dogs, and rats and into non-nephrectomized chickens, the plasma of the recipient animals acquired the ability to cause sustained elevation of blood pressure in nephrectomized cats, dogs, and rats, but not in non-nephrectomized chickens. A similar pressor effect active in cats and dogs was noted following the injection of human kidney extracts. The injection of chicken kidney extracts into chickens and cats failed to produce any SP in their plasma.

The sustained elevation of pressure following the injection of active plasma appears to be caused by continuous circulation of a rather stable pressor principle.

HECHT.

Folk, B. P., Zierler, K. L., and Lilienthal, J. L., Jr.: **Distribution of Potassium and Sodium Between Serum and Certain Extracellular Fluids in Man.** *Am. J. Physiol.* 153:381 (May), 1948.

The distribution of potassium and sodium between the serum and extracellular fluids was examined by flame photometer analyses. The mean distribution ratio of the potassium was only slightly lower than that for the sodium:

$$\text{mean } \frac{\text{K fluid}}{\text{K serum}} = 0.92; \quad \text{mean } \frac{\text{Na fluid}}{\text{Na serum}} = 0.96.$$

This discrepancy seems to be due to a loss of potassium from the cells to the serum during the process of obtaining and preparing the blood sample. The potassium distribution ratio here obtained is unexpectedly high, and since it approaches that of the sodium, it appears that part of the potassium is freely diffusible and is distributed across membranes according to the Gibbs-Donnan equilibrium in a manner similar to the sodium, chloride, and bicarbonate ions.

HECHT.

Ferraro, L. R., and Angle, R. G.: **Pheochromocytoma With Symptoms of Epinephrine Shock.** *Arch. Int. Med.* 81:793 (June), 1948.

A case of pheochromocytoma occurring in a 32-year-old soldier which did not present the classic symptoms usually associated with the disease, and which terminated fatally after "epinephrine shock," is reported. It appears that the syndrome during an "epinephrine crisis" results from an abnormal release of epinephrine into the general circulation and is characterized by hypertension, coldness of the extremities with blanching or mottling of the skin, diaphoresis, accelerated heart rate, dyspnea, and varying degrees of shock. Experimental, clinical, and pathologic evidence is submitted for the authors' explanation of this syndrome.

BERNSTEIN.

Packard, G. B., and Waring, J. J.: **Arteriovenous Fistula of the Lung.** *Arch. Surg.* 56:725 (June), 1948.

The presence of arteriovenous fistula in the lung has been recognized clinically only during the past few years. The steadily increasing number of cases reported suggests that it is much more common than supposed. The authors present a brief review of the literature, the pathologic process, and the symptoms and signs of this condition. The typical syndrome of cyanosis, clubbing of the fingers and toes, and polycythemia, without abnormality of the heart, plus the roentgenographic observations are practically diagnostic. Possible relationship of this condition to hereditary hemorrhagic telangiectasia is indicated, and the incidence of multiple lesions is emphasized.

One of the early cases in which the condition was recognized and treated surgically is reported. This case is the only one, as far as the authors know, in which pulmonary arteriovenous fistula was treated beneficially by single ligation of the pulmonary artery.

Discussion is made of the distinctive features of the pulmonary circulation as compared with the systemic circulation, which may permit some variations in treatment of pulmonary arteriovenous fistula as compared with treatment of fistula in the systemic circulation. Apparently arterial connection between the pulmonary artery and bronchial artery branches is hardly to be compared with the free collateral circulation existing in the systemic circulation.

BECK.

Rasmussen, H., and Moe, T.: **Pathogenesis of Left Bundle Branch Block.** *Brit. Heart J.* 10:141 (July), 1948.

The authors investigated a series of 100 patients with permanent left bundle branch block in an attempt to determine how often left bundle branch block is associated with heart disease causing enlargement of the left ventricle and how often conditions occur that may be supposed to produce a local lesion of the branch.

Seventy-six of the 100 patients studied had left-sided heart disease of aortic or hypertensive nature. Three had myocardial infarction, six were arteriosclerotic, one had a melanocarcinoma, and fourteen presented etiologies of uncertain nature. As determined by x-ray studies or necropsy, forty-five had gross cardiac enlargement, nineteen medium, nineteen slight, and seven no evidence for enlargement. Ten had neither an autopsy nor x-ray study. The average weight of the thirty-one hearts examined at autopsy was 652 grams. One weighed 1,780 grams. This is stated to be the largest heart ever reported.

From this study, it is seen that 72 per cent had disease of the left side of the heart and of those studied by x-ray films or necropsy, sixty-four (71 per cent) had left-sided enlargement of a degree sufficient to explain the bundle branch block. Therefore, left bundle branch block is five times more often to enlargement of the left heart than to a local lesion of the left branch of the bundle.

On the basis of this study and previous clinical and experimental studies, the authors believe that the electrocardiogram of left ventricular hypertrophy and that of left bundle branch block represent different degrees of retarded conduction of the left heart and the comprehensive term "electrocardiogram of left-sided retardation" is introduced to include all electrocardiographic patterns of retarded conduction of the left heart.

SOLOFF.

Newman, M.: Coarctation of the Aorta; Review of Twenty-Three Service Cases. Brit. Heart J., 10:150 (July), 1948.

The author presents an analysis of twenty-three patients suffering from coarctation of the aorta, twenty of whom served in the Second World War and three of whom served in the First World War. In this series, coarctation was first diagnosed between the ages of 19 and 37 years. When the condition was first recognized all were well-developed and well-nourished. All had elevated blood pressures in the upper extremities and lower blood pressures in the lower extremities. All had systolic aortic murmurs. Fifteen of the twenty-three persons had abnormal pulsations at the root of the neck, nine had visible collateral pulsations, twenty had an absent or small aortic knuckle, and eleven had erosion of the ribs.

Three of the twenty who served in the Second World War are dead. One died from rupture of the aorta after five years of military service. He had had no previous symptoms. One died on the operating table from cardiac failure during operation for the coarctation. One died of subacute bacterial endocarditis after six years of military service. All the remaining seventeen individuals are living. Of the three who served in the First World War, one died at 68 years of age. One was alive twenty-five years after the initial diagnosis but was receiving treatment for heart failure. The third, 54 years of age, was free of heart failure but was not able to walk far.

It is thus seen that the prognosis of coarctation of the aorta is not too bad if symptoms do not appear until after the age of 20 years, and that severe hypertension may last for many years without causing heart failure and some may live a normal span of life.

SOLOFF.

Harrison, C. V., and Lenox, B.: Heart Block In Osteitis Deformans. Brit. Heart J. 10:167 (July), 1948.

The authors report the clinical notes and findings at autopsy of two persons who had complete heart block complicating osteitis deformans. In one, a bar of calcification extended the length of the posterior mitral leaflet and had spread to the base of the interventricular septum. In the other, the posterior mitral leaflet was also calcified. All the aortic cusps, the aortic and mitral rings, and the upper posterior two-thirds of the membranous system were the seat of calcification. In a study of the hospital files and the literature, calcification in the heart was found in seventeen of forty-three cases of osteitis deformans (39 per cent) compared to a control series of 8 per cent.

It is concluded that calcification in the heart is five times as common in Paget's disease as in a comparable control series. Heart block is regarded as a complication of this propensity for Paget's disease to develop calcification and progressive fibrosis. The authors state that Paget's

disease affects the heart by tending to produce: (1) high cardiac output; (2) arterial calcification; (3) thoracic deformity; (4) valve calcification; and (5) heart block.

SOLOFF.

Kay, H. B.: Ventricular Complexes in Heart Block. *Brit. Heart J.* 10:177 (July), 1948.

To investigate the form of the ventricular complexes present in complete heart block, 100 instances of complete A-V block were studied. In fifty-two the etiology was coronary artery disease; in twenty, congenital; in three, rheumatic fever; in two, diphtheria; in one, syphilis; in one, pneumonia; in two, neurological disease; and in nineteen, the cause was uncertain.

The ventricular complexes were classified into (1) supraventricular pattern, (2) bundle branch block pattern, and (3) varying complexes.

Supraventricular Pattern.—This type was present in forty-seven patients. In nineteen the etiology was congenital; in eleven, coronary artery disease; in four, rheumatic fever or diphtheria; in one, pneumonia; in one, neurologic disease; and in eleven, doubtful. This type occurs when the pacemaker is situated in the main bundle and the branches function normally. This is the rule in congenital heart block. It may also occur as a result of lesions of both bundle branches either because a pacemaker is present in each bundle and both act synchronously or because one pacemaker sends impulses directly through the interventricular septum. This "bilateral missed block" is usually present when there is coronary artery disease, a relatively slow inherent rate, and association of supraventricular complexes with widened ones or occurrence of periods of sinus rhythm with bundle branch block.

Ventricular Complexes of Bundle Branch Block Pattern.—Of forty-seven instances, block of the right bundle branch was present in twenty-nine. Of these, twenty had coronary artery disease; five, myocardial infarction; one, neurologic disease; and three were of doubtful etiology. Block of the left bundle branch was present in six patients. Of these, three had coronary disease; one, congenital heart block; one, rheumatic heart disease; and one was of doubtful etiology. The block was of the concordant type in two; one of the common, and one of the uncommon type.

The pacemaker shifted between the left and right bundles in four patients. Widened ventricular complexes assumed varying patterns in six patients. This may be due to shifting pacemaker, conducted auricular impulses, or ventricular extrasystoles.

Thus, it can be seen that complete heart block with supraventricular complexes is most commonly seen in congenital heart block. The heart rate is faster, Adam-Stokes attacks less common, and the prognosis is better than in complete heart block with widened QRS complexes of the bundle branch block pattern which occurs more commonly in coronary artery disease or other forms of acquired heart disease.

SOLOFF.

Walls, E. W.: The Regenerative Capacity of Mammalian Heart Muscle. *Brit. Heart J.* 10:188 (July), 1948.

The opinion most generally held is that hyperplasia of cardiac muscle does not occur. Because of an occasional contradictory statement, the author thought it desirable to study the regenerative power of the myocardium of the rabbit. In adult rabbits the heart was exposed under anesthesia and a severe burn made in the lower third of the left ventricle by the application of the head of a nail, 5.0 mm. in diameter, heated to dull redness. The chest wound was closed and the animals were allowed to survive for periods ranging from three days to three months. No evidence of regeneration of cardiac muscle was observed in the histologic examination of serial sections.

SOLOFF.

Peel, F. A. A.: Tuberculous Pericarditis. *Brit. Heart J.* 10:195 (July), 1948.

The author reports eight instances of pericarditis of tuberculous origin. The diagnosis of tuberculosis was confirmed at autopsy in two patients. In two, the diagnosis was made by the finding of an associated active, primary subpleural Ghon lesion. In two, the diagnosis was made by demonstration of associated pleural effusions, in one of which tubercle bacilli were found. In one, the diagnosis was suspected on the basis of bilateral pleural effusion. In the last case, the diagnosis was suspected on the basis of a primary pericardial effusion with cardiac tamponade and fever.

On the basis of his observations, the author believes that the incidence of tuberculous pericarditis has been considerably underestimated. He believes that it arises in the early stage of dissemination of tuberculosis. It is frequently secondary to tuberculous mediastinal lymphadenopathy. Constitutional symptoms such as loss of weight, night sweats, and fever are relatively insignificant. Local symptoms of precordial pain or cough due to pressure may be present. Cardiac tamponade may occur. The striking physical finding is a persistent loud friction rub widely distributed over the precordium. Those instances in which tubercle bacilli cannot be recovered from the pericardial sac have a much better prognosis than those in which the organisms are recovered.

Tuberculous pericarditis may pass through four stages: (1) dry stage; (2) stage of effusion; (3) stage of absorption; and (4) stage of pericardial constriction. Arrest or cure may occur before the stage of effusion or after the stage of absorption. Because the rate of recovery is not known, it is not possible as yet to assess the value of treatment.

SOLOFF.

Peters, J. P.: The Role of Sodium in the Production of Edema. *New England J. Med.* 239:353 (Sept. 2), 1948.

This article presents in highly concentrated form a critical analysis of a broad range of investigative data, old and recent, bearing upon the physiologic disorders involved in the development of heart failure and edema. The Starling concept of hydrostatic pressure and colloid osmotic pressure as opposing forces governing the motions of fluid between capillaries and adjacent spaces is reviewed. Evidence is cited supporting the universal application of this hypothesis in the interpretation of edema formation. The author considers measurements purporting to demonstrate the inapplicability of the concept under certain conditions a reflection upon the measurements and not upon the validity of the principle.

Extracellular fluid escapes not only through the capillary wall but also through the lymphatics, which normally carry off the small amount of protein which has passed the capillary membrane or has been delivered from the cells. The stubborn character of the edema of lymphatic obstruction is the result of accumulation of this extracellular protein.

In the liver and portal circulation, the capillary walls are permeable to protein. Since the capillary pressure in this system is very low, fluid transudation could not be accomplished without a high colloid osmotic pressure of the extracellular fluid. There is, therefore, a continuous flow of plasma protein into the extracellular fluid of the portal bed; this returns to the general circulation in the thoracic duct. Since dye methods for plasma volume determination are based upon the distribution of protein-bound dyes, and since an unmeasurable quantity of the dye is constantly being lost from the circulation through the portal extracellular pathway, "it should be evident to reasoning persons that the method can have no value."

The water exchange between cells and extracellular fluid is governed by the osmotic pressure of the latter, which is, in turn, a function of sodium concentration. When the latter is low, the cells swell with water; when it is high, fluid is extracted from the cells.

Of the total glomerular filtrate formed, only about 1 per cent of water and less than 1 per cent of the sodium chloride is ordinarily excreted. The reabsorption of each is in large measure independent of the other. In the proximal tubules, about 80 per cent of the water and a roughly equivalent amount of chloride and of sodium is reabsorbed. Reabsorption of sodium is greater than that of chloride, reducing the sodium chloride ratio 1.3/1.0 to 1.0/1.0. In the loops of Henle, the reabsorption of sodium and chloride is very active, converting the altered filtrate from an isotonic to a hypotonic solution. In the distal convoluted tubule, water reabsorption is predominant, resulting in a hypertonic urine as finally elaborated.

Sodium reabsorption has top priority and is independent of water excretion. Conversely, water excretion is dependent upon the solutes in solution in the distal tubule. Thus, depending upon the amount of sodium remaining in the fluid after passage through the loop of Henle, water reabsorption is impeded. The damaged kidney has impaired sodium reabsorption ability and must, therefore, have impaired water reabsorption function.

Water reabsorption in the distal tubule is under the control of the pituitary antidiuretic prin-

ciple, which is present in large quantities in the urine during dehydration and pathologic edema states. If salt is given with water, the antidiuretic principle cannot prevent diuresis.

Sodium reabsorption is probably controlled by a steroid derived from the adrenal cortex. Cortical extracts stop only abnormal sodium wastes, whereas the synthetic steroid desoxycorticosterone acetate causes sodium retention in the normal subject.

Sodium excretion is powerfully influenced by factors other than the serum concentration. The dehydrated patient may have hypernormal serum sodium concentration, yet excrete very little. This has the physiologically desirable effect of extracting water from cells and permitting excretion of other substances without waste of water. Elaboration of the antidiuretic principle is promoted by increased solutes, especially sodium, in the serum. Hypernatremia also stimulates thirst. It is almost always a sign of dehydration, because if given the opportunity, the animal will dilute the sodium level back to normal by drinking. In diabetes insipidus, deprivation of water results in very high sodium and chloride levels. If the subject is given additional saline, the degree of dehydration is exaggerated.

According to the Starling concept, cardiac edema arises in the following sequence: Increased venous and capillary pressure, transudation, hemoconcentration, retention of salt and water. "This seems a logical sequence, compatible with existing physiologic theory." According to the "forward failure" concept of Warren and Stead, the primary event is retention of salt and water, followed by expansion of plasma volume, increased venous and capillary pressure, and transudation. The premises upon which this concept is based are examined. The demonstration of the plasma volume increase was based on the dye method, which is severely criticized by the author. Those who have carried it to the point of denial of the application of the Starling hypothesis in cardiac edema "deserve no consideration." Landis has shown that back pressure in the capillaries is not delayed until gross sodium retention has occurred. In borderline failure, edema may develop only when the legs are dependent. This edema formation is attended by hemoconcentration. The reasons must be found for blood volume expansion and simultaneous sodium retention if the "forward failure" concept is correct.

In hypoalbuminemia, transudation is followed by diminished blood volume, sodium retention, hypernatremia, and water retention through the activity of the antidiuretic principle. In cardiac edema, capillary pressure elevation may be substituted for hypoalbuminemia as the basis for transudation. Thereafter, the sequences are essentially the same. The administration of mercurial diuretic to the cardiac patient by inhibition of sodium reabsorption, is analogous to the administration of albumin to the nephrotic patient, which, by expansion of blood volume, removes the stimulus to sodium retention.

The author believes that the degree of blood volume expansion in heart failure has been exaggerated. Hepatic engorgement is precisely the condition to give fallacious blood volume determinations by the dye method. As evidence that diuresis in heart failure is regularly accompanied by an increase in plasma volume, the plasma specific gravity studies of Stewart are cited. The most striking diuresis reported by Merrill and Stead was associated with a sharp drop in hematocrit. Loss of circulating fluid is undoubtedly a characteristic of paroxysmal dyspnea and of coronary occlusion. Venesection in these patients is severely condemned. The reported beneficial effects of hypertonic glucose and of blood transfusions are noted.

If the earlier physiologic argument is adhered to, the rationale of salt restriction in cardiac or nephrotic edema is clear. The relative ineffectiveness of water restriction is also explained. Dehydration stimulates sodium retention, which in turn stimulates elaboration of the antidiuretic principle.

If hypernatremia were a primary event in heart failure, mercurial diuresis should be the logical first measure of treatment, as has been advocated. The author has found subnormal sodium levels in some patients in failure; in these, mercurial diuretics are distinctly contraindicated. The suggestion is made that in some patients in heart failure salt administration may be beneficial.

The author concludes that plausibility is no substitute for sound reasoning based upon fundamental scientific principles; that generalization from particulars is dangerous; and that no single organ or system in a complex integrated organism can be considered *in vacuo* apart from the whole.

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GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASE

Applications for research fellowships and fellowships for established investigators must be filed not later than September 15, 1949.

The majority of the research funds will be devoted to supporting individuals. A limited number of applications for grants-in-aid for research studies in the cardiovascular field and in basic research will be accepted until December 15, 1949.

Fellows desiring research grants-in-aid should submit such applications at the same time as the application for fellowship.

Further information, brochures, and application blanks may be obtained by writing the Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y.

ADDITIONAL GRANTS-IN-AID

Eleven awards for grants-in-aid, approximating \$50,000, were approved by the Board at its June meeting, as follows:

Mary C. Colglazier (University of Kansas); E. Watkins, Jr. (University of Oregon); J. R. Di Palma (Long Island College of Medicine); J. J. Sampson (Harold Brunn Institute for Cardiovascular Research, San Francisco); J. H. Heller (Yale University); H. C. Wiggers (Albany Medical College); H. L. Blumgart (Harvard University); W. C. Sealy (Duke Hospital); W. T. Salter (Yale University); C. R. Houck (University of Tennessee); H. C. Bazett (University of Penna.)

AMERICAN FOUNDATION FOR HIGH BLOOD PRESSURE BECOMES SECTION OF SCIENTIFIC COUNCIL

A plan of integration with the American Foundation for High Blood Pressure was approved at the June meeting of the Board of Directors. The Foundation will become one of the constituent Sections of the Scientific Council and will be known as the Council for High Blood Pressure Research.

A preliminary agreement approved by the Boards of both organizations provides for a joint staff study to recommend methods of integrating personnel and operations.

Alva Bradley, of Cleveland, Ohio, Chairman of the Board of Trustees of the American Foundation for High Blood Pressure, was elected a Member of the Board of Directors and of the Executive Committee.

FINANCIAL SUPPORT VOTED

Contributions of \$2,500 each were voted by the Board for the International Cardiological Congress, to be held in Paris September 3 to 9, 1950, and for the newly formed Interim Commission on Chronic Illness. An additional \$1,000 was voted this Commission by The American Council on Rheumatic Fever.

Regarding the latter group, the following resolution was passed:

"The Board of Directors of the American Heart Association, being aware of the formation of the Commission on Chronic Illness under the sponsorship of the American Medical Association, American Hospital Association, American Public Health Association, and the American Public Welfare Association, and recognizing the mutuality of interests and the common objectives of the American Heart Association, and the Commission as regards the problem of chronic illness,

"HEREBY RESOLVES to contribute the sum of \$2,500 to help meet the budget of the Commission for the year July 1st, 1949-June 30, 1950, as evidence of its desire to endorse, support, and participate in the program of the Commission on Chronic Illness.

"IT FURTHER RESOLVES, that the President of the American Heart Association be authorized to address a letter to local heart associations and the various sections and councils of the American Heart Association urging them to cooperate in all appropriate ways with the work of the Commission, and specifically presenting to them the opportunity for contributing financially to the Commission in the name of the American Heart Association, its councils, sections, and local affiliates."

American Heart Journal

VOL. 38

SEPTEMBER, 1949

No. 3

Original Communications

MEASUREMENT OF REGIONAL CIRCULATION BY THE LOCAL CLEARANCE OF RADIOACTIVE SODIUM

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THE dynamics of the blood-tissue exchange of a diffusible, inert substance has recently assumed significance as a basis for measurement of blood flow. The nitrous oxide method for the determination of cerebral blood flow¹ makes use of the time-concentration curves of this gas in arterial and cerebral venous blood. Where the tissue uptake of a substance is rendered measurable by the use of radioactive isotopes, it may be possible to estimate blood flow without resort to blood sampling. On this basis, measurement of peripheral blood flow has been proposed by Smith and Morales,² using radioactive krypton, and by Smith and Quimby,³ using radioactive sodium. In both cases a mathematical analysis of the saturation curves in the forearm or foot for the purpose of calculating blood flow in these regions is rendered extremely difficult by the variety of tissues involved in the measurements. Smith and Morales were able to approximate quantitative results by assuming in their analysis a constant arterial concentration of radioactive krypton. When, however, the arterial curve is variable, as is the case with the intravenous administration of radioactive sodium,³ mathematical analysis becomes almost hopelessly complex and requires, at best, a complicated integration involving the arterial curve obtained from serial blood samples. Smith and Quimby have not attempted an analysis of their sodium uptake curves but have employed them as a qualitative test of peripheral circulation. Both of these methods share the further disadvantages of exposing the entire body to radiation intensity equal to that necessary in the small segment under study, of requiring at least thirty minutes for a single measurement, and of being incapable of demonstrating rapid serial changes in blood flow.

If the diffusible tracer substance, instead of being administered in the general circulation, be introduced into the tissue in question, it is apparent that its clearance from the tissue will depend upon, and possibly be a measure of, the local tissue circulation. In fact, this very principle was utilized three years ago as a

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This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

qualitative demonstration of the adequacy of local circulation.⁴ The quantitative implications were not apparent to me until Dr. J. M. Crismon, of Stanford University, pointed out that in such a situation the arterial concentration might be neglected. On this basis I was able to make a simple mathematical analysis of the clearance of an injected substance.

Consider a small unit mass of the tissue into which the diffusible tracer (Na^{24} ion) has been injected. Let S represent its sodium space (extracellular volume); F_A , F_V , and F_L , the respective arterial inflow, venous, and lymphatic* outflow per minute; C_S , C_A , C_V , and C_L , the respective Na^{24} concentrations in S , arterial and venous blood, and lymph; and Q , the total content of Na^{24} in the unit mass of tissue.

In a short period of time (dt) there is a flow of venous blood ($F_V dt$) and of lymph ($F_L dt$) out of the tissue and a flow of arterial blood ($F_A dt$) into the tissues. The change in Q during this period would be equal to the quantity brought to the tissue by the arterial blood less the amount carried away in the venous blood and lymph or,

$$dQ = F_A C_A dt - F_V C_V dt - F_L C_L dt$$

The arterial concentration of Na^{24} will be negligible, representing a small quantity diluted by the entire cardiac output and, indeed, by the extracellular space of the body whence,

$$\frac{dQ}{dt} = -F_V C_V - F_L C_L$$

but $C_V = m C_S$ and $C_L = n C_S$

where m and n are constants with values between 0 and 1 and express the extent to which capillary blood and lymph come to equilibrium with the tissue concentration of Na^{24} . They depend on the diffusion rate of the ion, diffusion distances, capillary-tissue interface, on the proportion of arteriovenous shunts or other nonfunctional blood flow, and on the filtration and absorption of extracellular fluid at the capillary. Therefore,

$$\frac{dQ}{dt} = -F_V m C_S - F_L n C_S = -C_S (m F_V + n F_L)$$

but, $C_S = \frac{Q}{S}$, whence

$$\frac{dQ}{dt} = -Q \left(\frac{m F_V}{S} + \frac{n F_L}{S} \right)$$

which may be solved for Q :

$$Q = Q_0 e^{-kt}$$

where Q_0 represents an initial amount of Na^{24} and $k = \frac{m F_V}{S} + \frac{n F_L}{S}$

*In a previous description of this method⁵ the author chose to neglect lymphatic drainage on the basis that it constituted a very small fraction of the total drainage. Its inclusion at this time makes the analysis somewhat more rigorous but does not change the fundamental concepts.

or the sum of the effective blood and lymph flow per volume of extracellular water of the tissue in question. Since F_V and F_L are both constant fractions, (r) and $(1-r)$, of F_A under any one set of physiologic circumstances, we have:

$$k = \frac{mrF_A + n(1-r)F_A}{S} = F_A\Theta$$

where $\Theta = \frac{mr + n(1-r)}{S}$ and represents the net effectiveness of the

circulation as a renewal mechanism.

Thus, if the basic reasoning is valid, the tissue deposit of Na^{24} should decrease along a single exponential curve, which, if plotted semilogarithmically, should yield a straight line whose slope (clearance constant or k , above) is a quantitative measure of the total ability of the local circulation to remove and, by the same token, to supply freely diffusible substances.

METHOD

For testing the applicability of the theory developed above, the human gastrocnemius muscle was chosen as a suitable site. A small quantity of Na^{24}Cl (5 μc . in 0.5 to 1.0 c.c. of isotonic saline) is injected at a depth of about 2.0 cm. into this muscle by means of a fine needle. A Geiger-Müller counter, shielded with 5 cm. of lead except for one face, is placed next to the calf with the opening directed toward the site of injection, and counts are recorded at one-minute intervals until the counts per minute become too low for significant measurement. Neither the dose injected nor the geometry of the system is critical so long as the relations between injection site and counter tube are preserved during any one measurement. The counts per minute less background (final plateau reached after clearance) and corrected for decay of Na^{24} are plotted semilogarithmically against time and a straight line drawn through the points. The slope of this line yields the value for k or,

$$k = \frac{\log C_1 - \log C_2}{.4343 (t_2 - t_1)}$$

where C_1 and C_2 equal counts per minute at t_1 and t_2 , respectively. The time interval $(t_2 - t_1)$ should be long enough to permit a valid average slope to be drawn (about ten minutes). If the circulation should change significantly during the clearance and the change persist for a period of several minutes, this will be reflected in a corresponding change in the clearance constant during that time.

RESULTS

In all cases where nothing was done to alter the circulation, the clearance followed a simple exponential curve (Fig. 1), indicating the validity of the theoretical derivation and the assumption on which it was based. In a small series of eight such clearances on the resting muscle in different individuals the mean clearance was 5 per cent per minute (Table I). This value for the normal

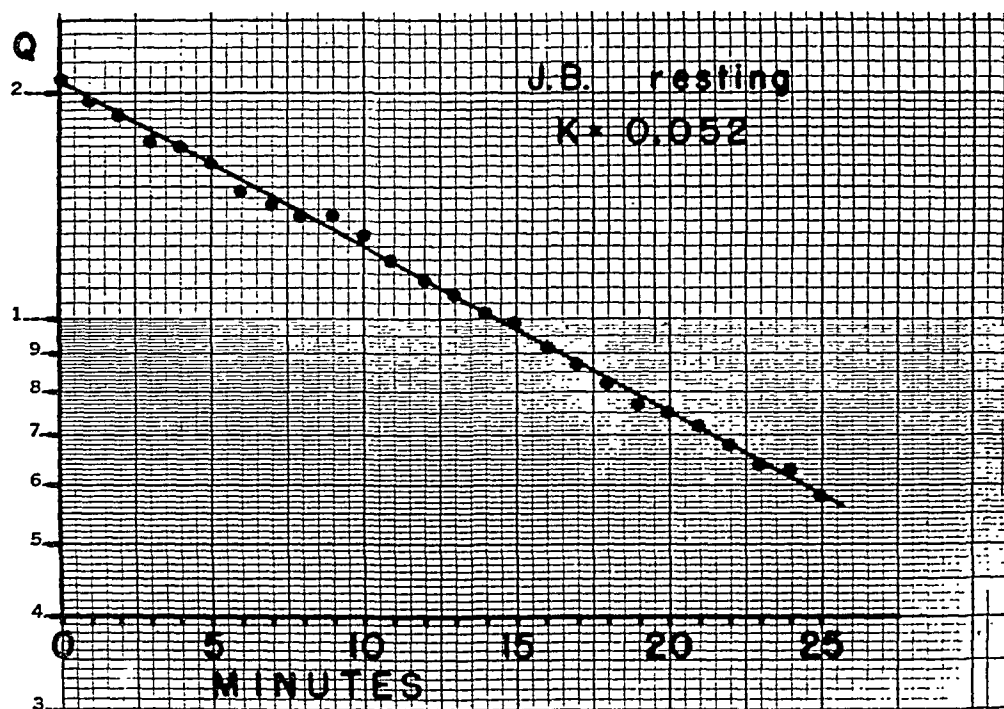


Fig. 1.—Counts per minute of Na²⁴ plotted semilogarithmically against time for a normal resting human gastrocnemius. The actual counts have been divided by an arbitrary factor (in this case 3,200) for convenient plotting.

Na clearance of the human gastrocnemius has recently been confirmed by others.⁶ To test the responses of the clearance constant to alterations in the circulation, some studies were done in which a control period was followed by some procedure designed to speed or slow the local circulation. The application of a tight tourniquet above the knee (Fig. 2, Table I) was invariably and immediately followed by a sharp reduction in the clearance constant to practically zero. Release of this tourniquet after ten minutes was associated with a clearance more than twice normal, undoubtedly a reflection of reactive hyperemia. Exercise of the gastrocnemius for one minute was accompanied and followed by a

TABLE I. GASTROCNEMIUS RADIOSODIUM CLEARANCE CONSTANTS

PATIENT	RESTING	TOURNIQUET	REACTIVE HYPEREMIA	AFTER 1' EXERCISE
J. B.	0.052	0.000	0.077	0.142
A. C.	0.044	0.005	0.111	0.104
T. M.	0.046	0.000	0.133	
E. J.	0.066	0.002	0.173	
C. S.	0.065	0.005	0.104	
M. F.	0.033			
A. R.	0.064			
H. B.	0.033			0.092
Mean	0.050	0.002	0.120	0.113

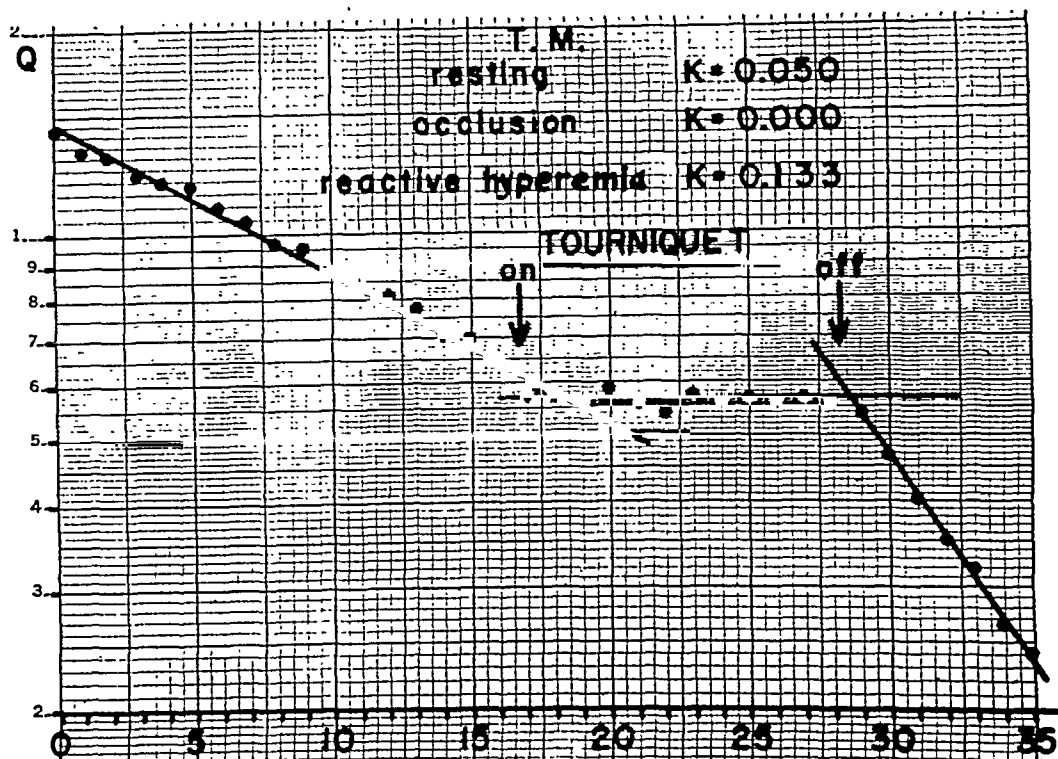


Fig. 2.—The effect of an arterial tourniquet about the thigh, and of reactive hyperemia on the clearance of Na^{24} from the human gastrocnemius.

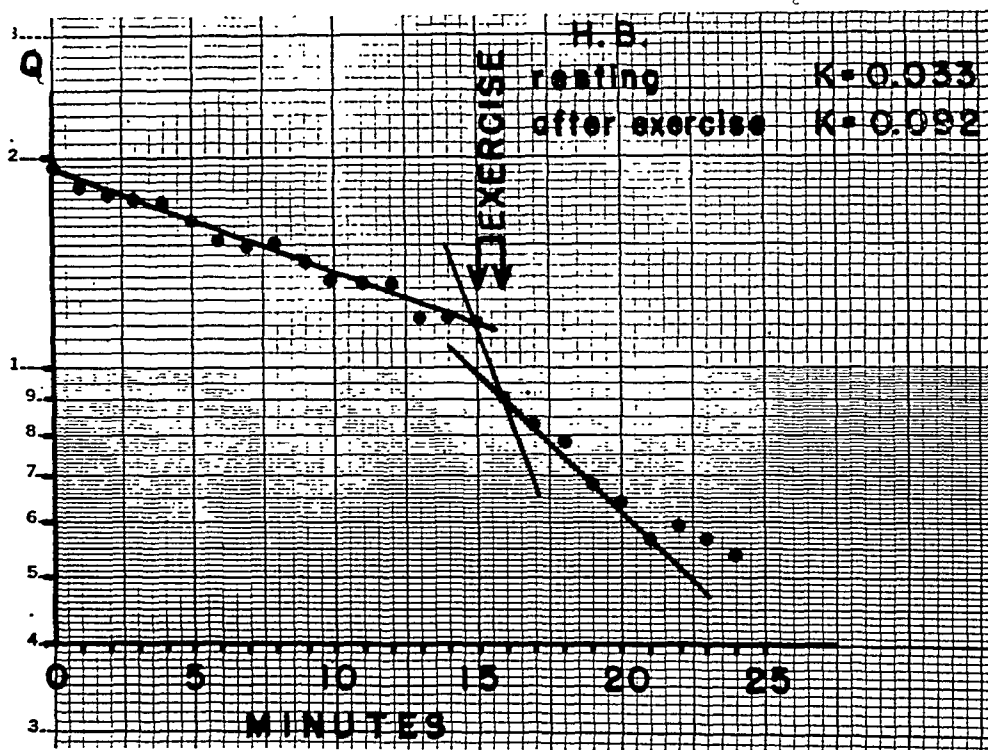


Fig. 3.—The effect on one minute's repetitive extension and flexion of the ankle on clearance of Na^{24} from the human gastrocnemius.

considerable increase in the clearance rate (Fig. 3, Table I). The local vasoconstrictor action of epinephrine was demonstrated by adding 0.1 mg. of the hydrochloride to the Na^{24}Cl before injection. This resulted in a decrease in clearance to less than one-sixth the resting value (Fig. 4).

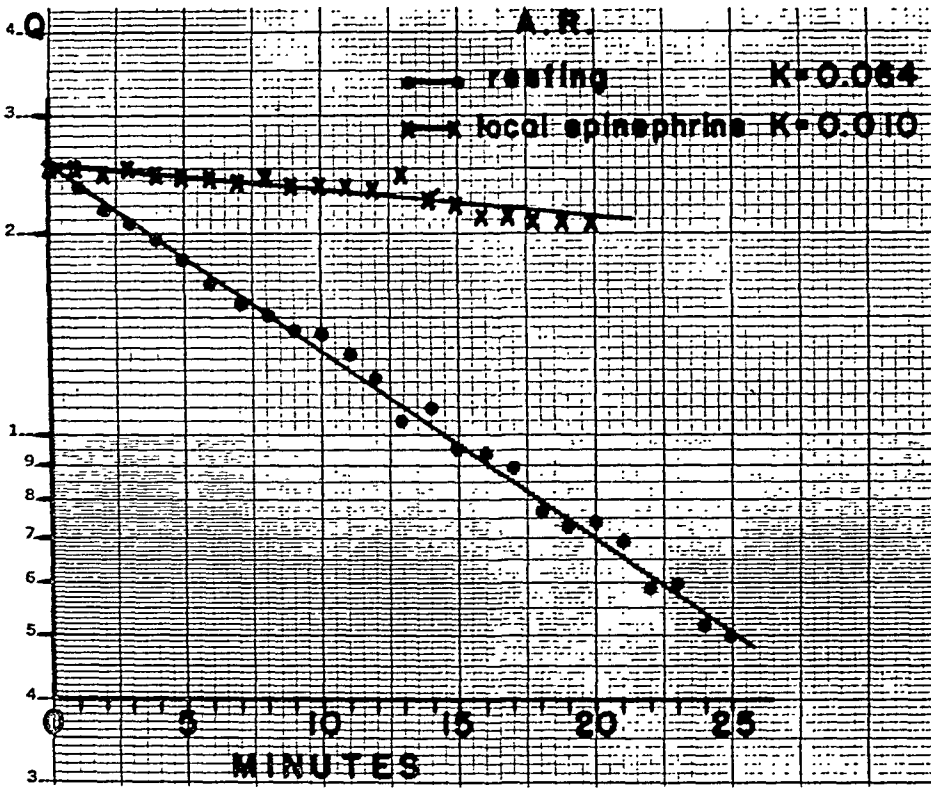


Fig. 4.—The effect on clearance of the addition of a small amount of epinephrine to the injected Na^{24} compared with the clearance of Na^{24} without added epinephrine in the same muscle.

DISCUSSION

The method appears to offer a convenient and clinically useful means for the measurement of effective circulation in a particular tissue. Since only about ten minutes are required for the accurate definition of a clearance rate and since a single injection permits twenty to thirty minutes of counting, it is possible to obtain at least two determinations from each injection. The infinitesimal dose of radioisotope required prolongs the useful life of the Na^{24} to the extent that an initial supply of 10 mc. may be used in these studies for nearly a week despite its very short half life of fifteen hours.

There is evidence to indicate that diffusion is of relatively little importance in the clearance of some tissues, in which case k would be an approximation to capillary blood flow. It seems preferable to the author, however, to retain the theoretical significance of k as a clearance constant rather than a rigorous measure of blood flow, a concession to exactness which does not compromise its value as a measurement of clinical importance. For intravascular blood flow is only one of

many factors involved in the homeostatic function of the circulation. In order to improve its nutrition a tissue may increase the flow of blood to itself but it is likely also to open closed capillaries, thus increasing diffusion interface and decreasing diffusion distances, or to increase filtration and resorption or accelerate the lymphatic circulation. It may well be argued that the effectiveness of the circulation in a tissue is better measured as its total ability to remove (and similarly to supply) freely diffusible substances. This total efficacy is accurately measured by the clearance constant, a concept which includes not only the volume flow of blood but also all the adaptations or disturbances which help or hinder the diffusion process. Although the sodium ion may be a less than vital contributor to cellular nutrition, its diffusion rate in aqueous systems is only slightly less than that of oxygen and carbon dioxide and more rapid than that of glucose,⁷ making it a fair representative of these more important constituents.

Although this technique utilizes only one-twentieth the total dose of Na^{24} employed by Smith and Quimby³ and therefore reduces proportionately the radiation throughout the body, it should be noted that the tissue immediately at the site of inoculation receives a considerably higher dosage. The most intense radiation is suffered by a sphere of tissue about 6 mm. in radius around the injection. With the help of a recent formula⁸ the amount of this maximum radiation (including both beta and gamma) was calculated for this tissue at the average clearance of 0.05 and was found to equal 0.5 equivalent roentgens per μc injected, or a total of 2.5 equivalent roentgens when 5 μc are used. A less rapid clearance would increase this radiation dose in inverse proportion. Since an ordinary roentgenogram of the calf produces a radiation dose of from 3 to 5 roentgens, the maximum radiation dosage from the Na^{24} employed in a tissue quite insensitive to radiation does not appear to be excessive.

The technique described should be applicable to tissues other than the gastrocnemius; indeed, to any tissue accessible to a hypodermic needle. Its use in the skin (by iontophoresis), the heart, liver, and uterus is now under study.

SUMMARY

A method is described for determining the clearance of radioactive sodium from its site of injection in a tissue. It is theoretically predicted and empirically found that the sodium remaining at the site of injection decreases along an exponential curve, the slope of which, plotted semilogarithmically, is a constant called the clearance constant. It is suggested that the clearance constant represents a valid and convenient measure of the local circulation in its broadest sense, and therefore a clinically useful determination.

REFERENCES

1. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, *J. Clin. Investigation* 27:476, 1948.
2. Smith, R. E., and Morales, M. F.: On the Theory of Blood-Tissue Exchanges. II. Applications, *Bull. Math. Biophysics* 6:133, 1944.

3. Smith, B. C., and Quimby, E. H.: Use of Radioactive Sodium as Tracer in Study of Peripheral Vascular Diseases, *Radiology* 45:335, 1945.
4. Nathanson, I. T., Nutt, A. L., Pope, A., Zamecnik, P. C., Aub, J. C., Brues, A. M., and Kety, S. S.: The Toxic Factors in Experimental Traumatic Shock. I. Physiologic Effects of Muscle Ligation in The Dog, *J. Clin. Investigation* 24:829, 1945.
5. Kety, S. S.: Quantitative Measurement of Regional Circulation by the Clearance of Radioactive Sodium, (*Proc. Physiol. Soc. Phila*, Jan. 20, 1948), *Am. J. M. Sc.* 215:352, 1948.
6. Cooper, F. W., Elkin, D. C., Shea, P. C., and Dennis, E. W.: The Study of Peripheral Vascular Disease With Radioactive Isotopes. Part II, *Surg., Gynec. & Obst.* 87:1, 1948.
7. Hitchcock, D. I.: In: Höber, Rudolf: *Physical Chemistry of Cells and Tissues*, Philadelphia, 1945, The Blakiston Company, p. 13.
8. Marinelli, L. D., Quimby, E. H., and Hine, G. J.: Dosage Determination With Radioactive Isotopes. II. Practical Considerations in Therapy and Protection, *Am. J. Roentgenol.* 59:260, 1948.

ARTERECTOMY IN THE TREATMENT OF INTRACTABLE PAIN FOLLOWING RECOVERY FROM ACUTE ARTERIAL OCCLUSION

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IN DECEMBER, 1946, there was referred to us for study a physician who, two months previously, had had a myocardial infarction followed in two weeks by an acute occlusion of the left popliteal artery. This arterial embolus came on suddenly, with coldness, blanching, numbness, and paresthesia of the left foot and lower two-thirds of the left leg. Over the next two weeks the color and temperature changes gradually improved, but the paresthesias and numbness persisted, and gradually there was added to these a new type of pain which was continuous, diffuse, and subject to spontaneous, severe exacerbations, and which it was very difficult for the patient to describe accurately. Most often he would characterize it as cramping in character; at other times he said it felt like a burning sensation. He thought that it was unrelated to activity, temperature, or emotional states. It did seem to come on more often at night. When the acute, spontaneous attacks came on, he seemed to be able to get some relief by grasping the foot and rocking back and forth on his bed, or by getting up and walking to and fro across the room until stopped by pain in the left calf.

Physical examination showed a limb with severe impairment of arterial circulation, dependent rubor, distal hypoesthesia (see Fig. 1), with a delayed pain response to strong stimulation (protopathic pain response), and no evidence of increased vasoconstriction. A left lumbar block with procaine was done and, although the temperature of the left toes fell (see Fig. 2), the left foot felt easier and no pain occurred during or after the block, except to a minor degree. An arteriogram (Fig. 3) showed a filling defect, with obstruction of the left popliteal artery at the level of the superior geniculate branch.

Here we are dealing with a patient with acute occlusion of a major artery and ischemic neuritis with severe, spontaneous pain which had many of the characteristics of causalgia. This pain was somewhat improved by a sympathetic block with procaine, but skin temperature measurements showed a decrease in blood flow at the time of injection.

Last year we reported our experience with three patients who had sustained an acute occlusion of a major artery as a result of thrombosis.¹ All those patients actually fitted into the picture which we are now describing. They gave no clinical evidence of increased vasomotor tone, but in each one there was temporary

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This work was aided in part by a grant from the Life Insurance Medical Research Fund.

Presented before the Twenty-first Annual Scientific Meeting of The American Heart Association, Chicago, Ill., June 18 and 19, 1948.

relief of severe rest pain following lumbar block. We feel now that the terrific pain and hypersensitivity which they developed in the months following the acute occlusion might well have been due to ischemic neuritis or to some type of

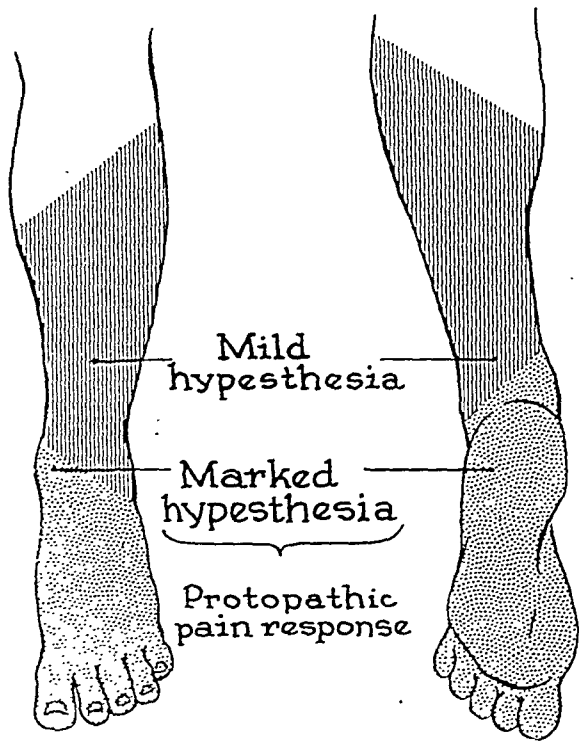


Fig. 1.—Sensory changes two months after acute arterial occlusion. Left popliteal embolus. December, 1946.

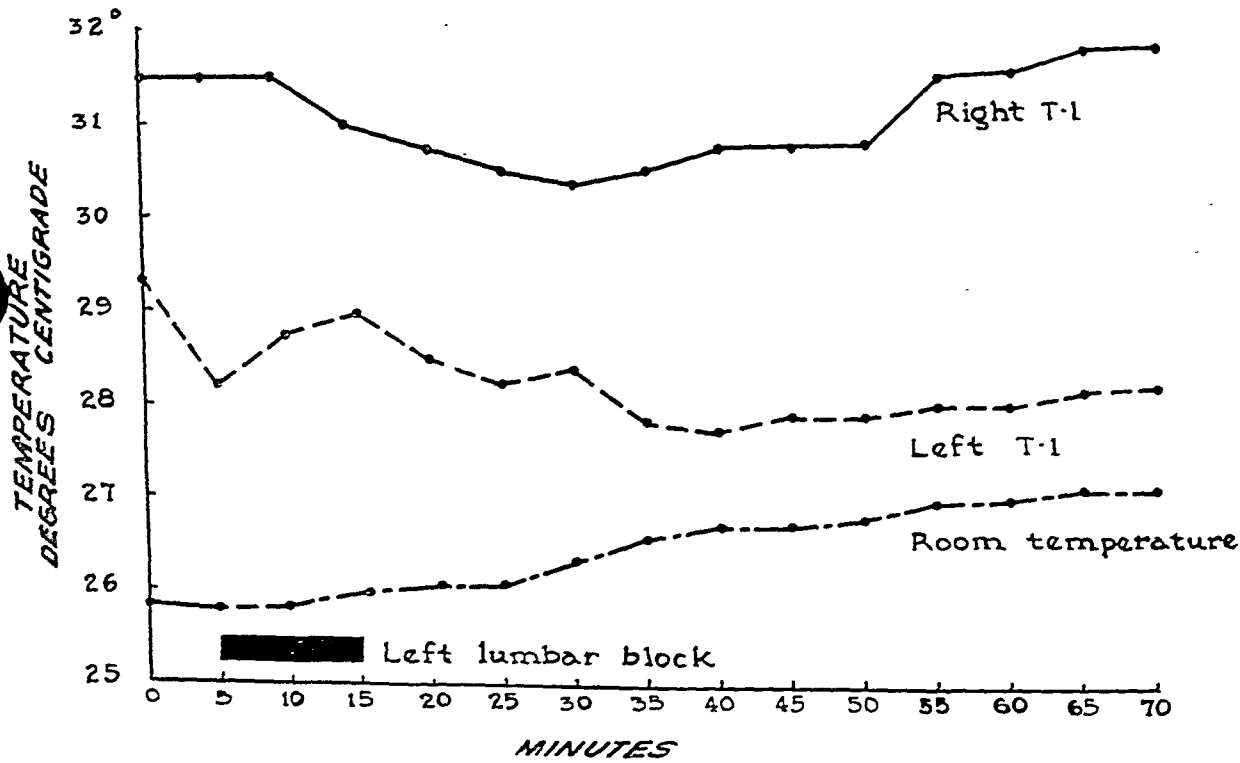


Fig. 2.—Lumbar block on skin temperature. Left popliteal embolus. December, 1946.

causalgia. In each case the relief of pain by lumbar block might have been attributed to the interruption of the sympathetic impulses, which is recognized to be effective in treatment of causalgia, rather than to any improvement in the supply of blood to the peripheral tissues. In each of these patients, lumbar sympathectomy was done, and brought relief of the rest pain of which they had complained. In each case, however, there was a rapid development of gangrene,



Fig. 3.—Filling defect with obliteration of left popliteal artery after embolic occlusion.

necessitating amputation of the involved leg. Similar cases have been described by Atlas.² We felt, therefore, that in the patient we are now discussing, lumbar sympathectomy, although it probably would have relieved the pain, was definitely contraindicated.

For the past twenty-five years Leriche³ has recommended periarterial stripping and arterectomy. He advanced the hypothesis that the artery at the

TABLE I. THE SYMPTOMS, THE RESULTS OF STUDIES, AND THE RESULTS OF ARTERECTOMY IN ELEVEN PATIENTS.

PATIENT	ARTERY INVOLVED	ACUTE OCCLUSION	ISCHEMIC NECROSITIS	PROTOPATHIC PAIN	DROP IN SKIN TEMP. WITH SYMPATHETIC PARALYSIS*	ARTERIOGRAPHY	ARTERECTOMY	RELIEF OF PAIN	OBJECTIVE IMPROVEMENT IN CIRCULATION	DEATH	AMPUTATIONS	FOLLOW-UP
1 C. G.	Left superficial femoral	+	+	+	0	+	None	0	0	0	0	24 mo.
2 P. S.	Left popliteal	+	+	+	+	+	Dec., 1946	+	0	4 mo.	0	4 mo.
3 W. L. B.	Right common femoral	+	+	+	0	+	Jan., 1947	+	0	0	0	17 mo.
4 A. McC.	Right popliteal	+	+	+	+	+	Feb., 1947	+	0	0	0	16 mo.
5 J. LeC.	Left superficial femoral	+	+	+	—	0	Sept., 1947	3 days	0	0	+	9 mo.
6 W. H.	Left superficial femoral	+	+	+	0	+	Sept., 1947	+	0	0	0	9 mo.
7 F. K.	Right common femoral	+	+	+	—	0	Oct., 1947	+	0	0	0	8 mo.
8 G. C.	Left superficial femoral	+	+	+	—	+	Nov., 1947	+	+	0	0	7 mo.
9 F. M.	Left superficial femoral	+	+	+	—	+	Jan., 1948	+	+	0	0	5 mo.
10 J. McE.	Right common femoral	+	+	+	—	+	Feb., 1948	+	0	9 days	0	9 days
11 M. C.	Right superficial femoral	+	+	+	0	+	May, 1948	+	0	0	0	1 mo.

*—means test not done.

site of occlusion may act as a trigger area for the production of pain and vasomotor disturbances. On the basis of this concept, a popliteal arterectomy was performed in our patient. The complete relief of the spontaneous pain was as surprising to us as it was gratifying to the patient. Postoperative studies failed to demonstrate objective improvement in the circulation. Numbness and paresthesia persisted. There was no improvement in intermittent claudication, but the patient was able to be up and around again. He returned to active practice until he died four months later of another myocardial infarction.

We have since then seen nine other patients with acute occlusion of a major artery, either by thrombosis or by embolism. The data on these patients are shown in Table I. There was recovery, as far as the viability of the extremity was concerned, in each case, but subsequently the patients developed intractable, diffuse pain and distal hypoesthesia, with a protopathic pain response. The pain was continuous, diffuse, and subject to severe spontaneous exacerbations. The patients described it variously as resembling a "toothache," or a "cramp," though they stressed that these terms did not quite describe the character of the pain. When asked to indicate how the pain differed from a toothache or a cramp, many of them mentioned the sensation of burning accompanying the pain. Some found relief in grasping the foot, and it was not unusual on ward rounds to find the patient gently rocking back and forth in the bed, tightly holding the affected foot. Dependency did not seem to help the pain. Walking appeared to ease it, though most of the patients stated that exercise was prevented by intermittent claudication. They all complained of numbness in the affected member. They all showed distal hypoesthesia and a delayed pain response, which Head has called the protopathic pain response. There was a peculiar emotional reaction to this delayed type of pain. The spontaneous pain seemed to be out of proportion to the degree of circulatory impairment. It might be relieved temporarily by lumbar sympathetic block.

With one exception, these patients have undergone an operative removal of the thrombosed segment. After operation there was relief of the severe spontaneous pain, though other types of pain due to ischemia might persist. Three of the patients spontaneously stated, a few minutes after the artery had been divided, that their pain was gone. One of the patients who had had such severe pain that he had requested an amputation, and who had slept only an hour at a time for almost a week, slept for sixteen hours immediately after the operative procedure. One patient had return of pain three days after the operative procedure, but stated that the pain was now different in character from that which he had experienced before surgery. This patient later developed severe venous thrombosis, with exacerbation of his arterial insufficiency, and a supracondylar amputation was necessary. Amputation of the leg was performed in only one other patient in this series. After arterectomy, although the spontaneous pain was relieved, this patient was incapacitated by hyperesthesia of the foot. There was marked atrophy of the soft parts, and a contracture of the knee developed. Two of the patients died from acute coronary occlusion, one of them nine days after surgery and the other four months after surgery. Neither of these, had had recurrence of his pain up to the time of his death. In one patient,

arterectomy was not done, but he has been treated with rest and vasodilators for two years. There has been no change in the character of his pain over this period of time.

The circulatory status of the affected limb was carefully evaluated in all these patients before and after surgery. In none of them has there been any objective improvement in the peripheral blood flow, although functional recovery in the postoperative period would suggest some improvement in circulation. In eight individuals there was no increase in the ability to walk, while in two there was some improvement over a period of months. The neurological findings have remained unchanged. There has been persistence of the subjective numbness and paresthia and persistence of the objective evidence of hypoaesthesia and the protopathic pain response.

Leriche³ rightly classifies the arterectomy as a conservative measure. It is a relatively minor procedure and can be done even in the poor-risk patient. All of the operations have been done under local anesthesia. In most cases we were content to remove small portions (from 2.0 to 3.0¹cm.)⁷ of the thrombosed vessel, although Leriche³ has recommended removal of the entire thrombosed segment, up to 25 centimeters. The exact site of obstruction was accurately localized preoperatively by Thorotrast arteriograms. We preferred to use Thorotrast in these patients with impaired arterial circulation because of the danger of vasospasm produced by Diodrast. In two cases the artery was found to be occluded in the area which was exposed for arteriography.

DISCUSSION

Periarterial sympathectomy was first advocated for the treatment of post-traumatic vasospastic conditions by Leriche⁴ in 1913. Subsequently he resorted to arterectomy in those cases in which the vessel was obliterated. He states: "It seems paradoxical to seek to improve the circulation in a limb which has been crippled by an arterial thrombosis by removing the obliterated segment." However, in spite of the circulatory arrest, after the thrombosed segment was removed, there was not only relief of pain but the quantity of blood reaching the periphery was augmented, the extremity became warmer, vasomotor disturbances disappeared, and, not infrequently, the pulse and oscillations reappeared. He feels that only one explanation is possible: the thrombosis modifies the state of the arterial wall, producing a state of centripetal excitation. He therefore defines an arterectomy as a sensory neurectomy which depresses the point of departure of vasomotor reflexes and permits the collateral circulation to achieve a state of vasodilatation. He feels that he has proved this experimentally through his work with Heitz.⁵ Clinically, he points to his 45 to 50 per cent long-term good results in 144 arterectomies in elderly patients with arteriosclerosis.

Leriche³ states that his worst results are in those patients with rubor and edema. His best results are in those who have intermittent claudication, rest pain, and rubor on dependency. He stresses the importance of preoperative arteriography, and feels that if in the arteriogram, the arterial segment distal to the thrombosis is not shown to be filled by the contrast medium, an arterectomy

would not be successful, but that if this distal segment is shown to be filled, the results will be excellent. He also stresses the importance of including all the thrombosed segment in the arterectomy, and he states that sometimes it is necessary to remove as much as 20 to 25 cm. of the superficial femoral artery. In our experience it has been necessary to remove only a short segment.

Recently Cooper⁶ has reported a case of obliteration of the bifurcation of the aorta. Oscillometry and skin temperature studies showed improvement in the circulatory status of the lower extremities after the bifurcation of the aorta had been resected.

In the experimental animal, Strömbeck⁷ was unable to demonstrate any significant increase in circulation after arterectomy. He produced thrombosis of arteries in dogs by means of trauma. Then, fifteen days to two and one-half months later, the segments were resected and arteriographic studies were done at intervals. Except in one case, no increased collateral circulation was demonstrated by arteriography.

In only two of our ten patients have we felt that there was objective evidence of increase in the circulation of the extremity after arterectomy. The improvement in circulation in these patients took place only some time after operation and was probably the result of a spontaneous increase in collateral blood flow. We do not believe that the relief of pain is the result of any improvement in circulation but rather that it is due to the interruption of some nervous reflex from the region of the thrombosed artery.

SUMMARY

After recovery from acute occlusion of a major artery to the extremity, even though the circulation is sufficient for tissue nutrition, the patient may develop severe rest pain with paresthesias and numbness of the extremity. This pain has been termed ischemic neuritis. Temporary relief may be obtained by blocking the sympathetic nerves to the leg, but sympathectomy is contraindicated. In a series of ten patients the site of obstruction was visualized by arteriography. Excision of a segment of the thrombosed artery was followed by immediate relief from the pain. There was no significant increase in circulation after this procedure. It is believed that arterectomy is of value in the treatment of this type of pain through the interruption of some nervous reflex which originates from the thrombosed artery.

REFERENCES

1. Freeman, N. E., Leeds, F. H., and Gardner, R. E.: Sympathectomy for Obliterative Arterial Disease; Indications and Contraindications, *Ann. Surg.* **126**:873, 1947.
2. Atlas, L. H.: Lumbar Sympathectomy in the Treatment of Peripheral Arteriosclerotic Disease, *AM. HEART J.* **23**:493, 1942.
3. Leriche, René: *Thromboses artérielle (Physiologie pathologique et traitement chirurgical)*, Paris, 1946, Masson et Cie., pp. 350-356, 385-391.
4. Leriche, R.: De l'élongation et de la section des nerfs périvasculaires dans certains syndromes douloureux d'origine artérielle et dans quelques troubles trophiques, *Lyon chir.* **10**:378, 1913.
5. Leriche, R., and Heitz, L.: De la Réaction vaso-dilatatrice consécutive à la résection d'un segment, *Compt. rend. Soc. de biol.* **130**:160, 1917.
6. Cooper, F. W., Jr., Harris, M. H., and Kahn, J. W.: Ligation and Division of the Abdominal Aorta for Metallic Embolus From the Heart, *Ann. Surg.* **127**:1, 1948.
7. Strömbeck, J. P.: Effets de la résection artérielle, *Acta chir. Scandinav.* **83**:510, 1939.

THE RELATIONSHIP OF ATHEROMATOSIS DEVELOPMENT IN THE CHICKEN TO THE AMOUNT OF CHOLESTEROL ADDED TO THE DIET

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A RTERIOSCLEROSIS of a type closely resembling that found in the human being appears spontaneously with advancing age in birds, as has been demonstrated by the classical work of Fox.^{1,a,b} The susceptibility of birds to atherosclerosis has been demonstrated by the induction of atheromatosis in these animals by the feeding of diets high in cholesterol. Dauber and Katz^{2,3} were the first to show that atherosclerosis could be consistently produced in the chicken by the feeding of a diet high in cholesterol. Since that time the chicken has been used by a number of investigators as a laboratory animal in the investigation of experimental atherosclerosis.^{6,7} It possesses certain advantages for this type of research because atherosclerotic lesions can be induced in a relatively short time and the induced lesions resemble the spontaneously occurring ones in many respects. Furthermore, the chicken is an omnivore, and normally ingests cholesterol-containing foods, thus avoiding the important objection which has been leveled against the rabbit and the guinea pig, species in which cholesterol is essentially a foreign substance. Dauber⁴ found that spontaneous arteriosclerosis developed in the chicken at the age of 5 to 6 months at the earliest: arteriosclerosis was found in 45 per cent of chickens over 1 year of age. It is obvious, therefore, that the chicken is a suitable animal for the experimental production of atherosclerosis if used before the age of 6 months, when spontaneous arteriosclerosis begins to occur. It is also a suitable animal for studies on the prevention of the spontaneously occurring disease.

Among the data which have accumulated to date, there are no studies undertaking to quantitate the effect of various concentrations of dietary cholesterol on the rapidity and degree of development of atherosclerosis in the chicken. Such information would obviously be of value in the establishment of controlled base lines for the carrying out of further special studies. Moreover, such studies might be of value in determining the degree to which the chick can dispose of dietary cholesterol. We have also utilized these studies to determine the relationship of dietary cholesterol concentration to the blood cholesterol levels and to ascertain the effect of various durations of such feedings.

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This study was supported by a grant from the Life Insurance Medical Research Foundation Fund.

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PROCEDURE

Four-week-old white Leghorn cockerels obtained from a commercial hatchery and known to be free of indigenous diseases were utilized. The animals were fed chick starter mash and tap water ad libitum for several days before the experiments were begun. Three series of experiments were run, lasting five, ten, and fifteen weeks, respectively. Each series consisted of five groups of twelve chicks each, making a total of fifteen groups and 180 chickens. In each series, the control group was maintained on chick starter mash and water. The four remaining groups received mash containing concentrations of 0.5, 1, 2, and 4 per cent cholesterol suspended in cotton seed oil, the oil making up 20 per cent of the diet by weight.

Animals were weighed weekly. Blood cholesterol determinations (total cholesterol) were made at weekly and biweekly intervals by the method of Schoenheimer and Sperry.⁸ All animals were sacrificed, and the thoracic and abdominal organs were examined. The hearts and aortas were removed en bloc, slit open with a fine scissors, and any gross atheroma recorded on a diagram and fully described. In some cases the pulmonary arteries were opened and examined, and in a few birds the brain was removed en bloc to permit examination of the cerebral vessels. Sections were taken routinely from the lungs, liver, pancreas, adrenals, spleen, and kidneys. The thyroid glands were carefully dissected, cleaned, and weighed. Specimens were preserved in formalin, sectioned, and stained with hematoxylin and eosin in standard fashion. A longitudinal section consisting of heart muscle and thoracic aorta and a separate section of the abdominal aorta were made and examined in all birds in which there was no clear evidence of macroscopic atheromatosis. Sections were also made of the thyroid gland, liver, kidneys, and spleen in occasional cases.

GRADING

Atherosclerotic lesions were graded on the basis of their gross and of their microscopic appearance. The grading ranged from 0 to 4 and was based on the extent and severity of the lesions. The highest grades were given to extensive lesions, yellow in color, raised, and calcified on gross examination, or to those which showed marked calcification, cholesterol clefts, abscess formation, and many foam cells on microscopic examination.

The grading is, of course, subjective and empirical, but is consistent throughout when done by a single observer unaware of the particular experimental grouping of the animal being autopsied, as in this study. Experience proved that the gross inspection correlated closely with the microscopic appearance, and that gross grading was the more reliable method, as it precluded the possibility of the section being inadvertently cut from an uninvolved portion of the aorta.

Livers were classified as fatty when they were grossly yellow and greasy in appearance and on cut section. The microscopic examination consistently confirmed the gross diagnosis.

RESULTS

A. *Observations on the Vascular Lesions.*—

1. *The Effect of Five Weeks' Feeding of a Cholesterol-Rich Diet:* The data are summarized in Table I and illustrated in Figs. 1 and 2. Only three of the twelve chickens on 0.5 per cent cholesterol showed gross lesions of the aorta, and in each of these the liver was definitely fatty. There was evidence of fatty liver in only two other birds in this group. The gross appearance of almost all the aortas suggested slight thickening of the intima, but there was no yellow discoloration, nor were there any discrete plaques, and these aortas proved to be normal on microscopic examination. The average gross grading for this group was: thoracic aorta, 0.15; abdominal aorta, 0.

TABLE I. EFFECT OF FIVE WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA		
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*
Control	0	0	0	0	0	0
0.5	25	0-0.5	0.1	0	0	0
1	66	0.5-2	0.7	8	0-1	0.1
2	75	0.5-2	1.3	33	0-2	0.4
4	100	0.5-4	2.0	33	0.5-2	0.5

*4 = Severe.

Eight of the twelve birds on a 1 per cent cholesterol regime showed gross arterial lesions grading from 0.5 to 2. The liver was grossly fatty in all birds in this group. The vascular lesions ranged from irregular yellow streaking of the brachiocephalic vessels and aorta (classified as Grade 0.5) to discrete, raised, yellow plaques in the thoracic aorta (classified as Grade 2). Only one bird showed a lesion of the abdominal aorta, which consisted of several whitish pin-point plaques. The average gross grading for this group was: thoracic aorta, 0.75; abdominal aorta, 0.10.

Nine of the twelve birds on 2 per cent cholesterol showed gross intimal lesions in the thoracic aorta, and four of these also had gross lesions in the abdominal aorta. All the animals had fatty livers. The lesions were more extensive and advanced than in the preceding groups. The average gross grading for this group was: thoracic aorta, 1.5; abdominal aorta, 0.5.

All the birds on 4 per cent cholesterol showed gross lesions of the thoracic aorta, ranging from Grade 1 to Grade 4 in classification. Four of these also had lesions of the abdominal aorta ranging from Grades 0.5 to 2. The liver was grossly fatty in all birds in this group, and many of the spleens showed whitish specks on cross section which proved on microscopic examination to be accumulations of foam cells. Some of the lesions were advanced. For example, in one

bird the brachiocephalic vessels showed numerous yellow, calcified plaques; the whole of the thoracic aorta was covered with a confluent pale yellow raised and ridged plaque; the semilunar valves showed marked involvement with thickening and plaque formation and there were also a few plaques on the mitral leaflets. The average gross grading for this group was: thoracic aorta, 2.0; abdominal aorta, 0.5.

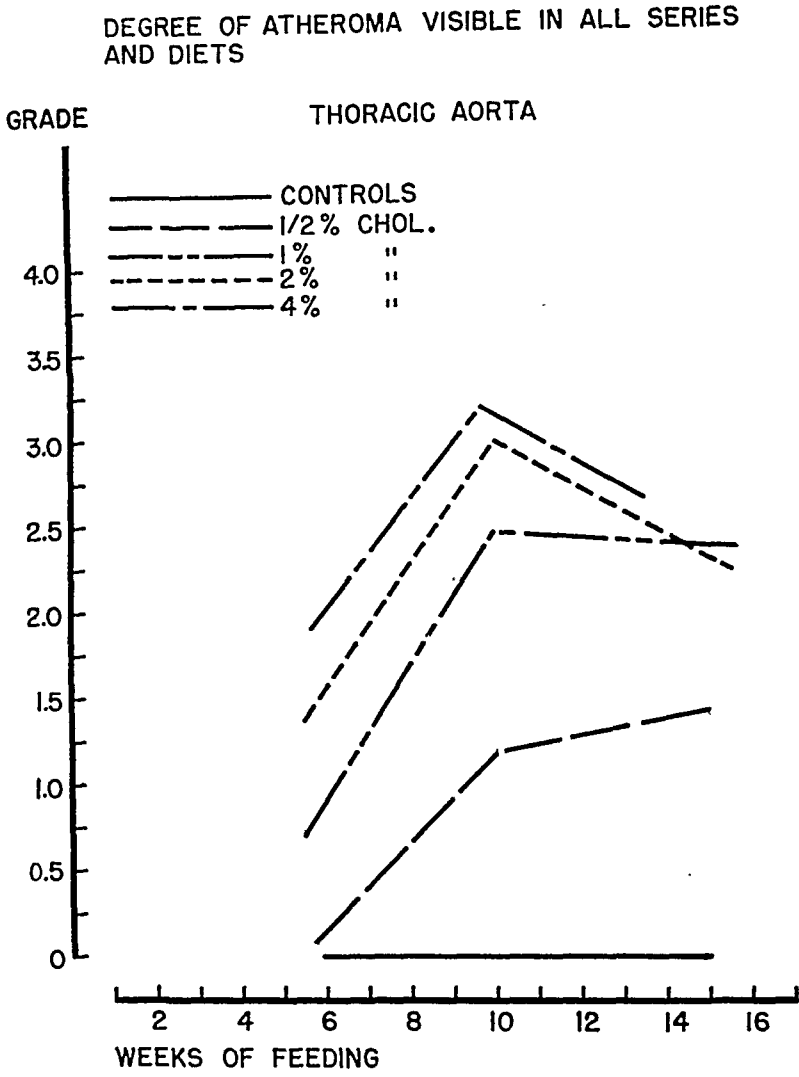


Fig. 1.

None of the birds in the control group showed gross lesions of the heart or aorta. The livers were normal in appearance, and no unusual findings in any of the other organs were observed.

To summarize, a progressive increase was found in the frequency of occurrence, severity, and extent of the lesions with increasing concentration of cholesterol in the diet. In the 0.5 per cent cholesterol group 25 per cent of the birds

had lesions in the thoracic aorta; in the 1 per cent group, 66 per cent; in the 2 per cent group, 75 per cent; and in the 4 per cent group, 100 per cent. There was a similar increase in the frequency of lesions in the abdominal aorta with increasing concentration of cholesterol in the diet. Thus, the percentage of animals showing gross lesions in the abdominal aorta ranged from 0 in the 0.5 per cent group to 33 per cent in the four per cent group. Gross atherosclerotic lesions

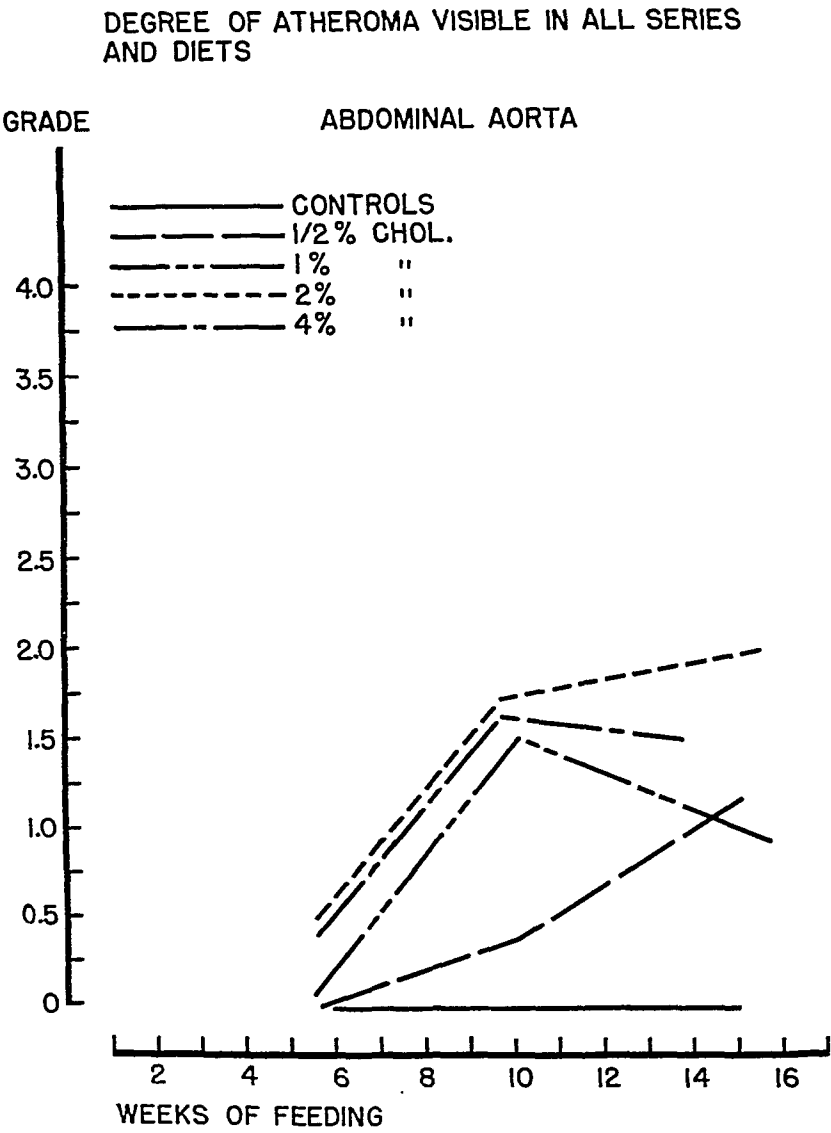


Fig. 2.

apparently can be produced in five to six weeks by the feeding of diets rich in cholesterol. The frequency of occurrence, severity, and extent of the lesions appears to be directly related to the concentration of cholesterol in the diet. Lesions of the abdominal aorta were less frequent and occurred only when the higher concentrations of cholesterol were fed.

2. *The Effect of Ten Weeks' Feeding of a Cholesterol-Rich Diet:* The data are summarized in Table II and illustrated in Figs. 1 and 2. As in the previous group fed for five weeks, there was an increased frequency of occurrence of lesions with increased concentrations of cholesterol in the diet. The 0.5 per cent cholesterol group showed 80 per cent of animals with lesions in the thoracic aorta, whereas all the other groups had lesions in the thoracic aorta in 100 per cent of animals. There was, further, a progressive increase in the severity of the lesions as shown by the empirical grading, which rose from 1.0 in the 0.5 per cent group to 3.5 in the 4 per cent group. The abdominal aorta showed a parallel increase in frequency and progression of lesions with increasing percentage of cholesterol, but as in the previous series, the time of occurrence and severity of abdominal lesions lagged somewhat behind the lesions of the thoracic aorta. None of the control animals showed atherosclerosis.

TABLE II. EFFECT OF TEN WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
Control	0	0	0	0	0	0	0
0.5	80	1-0.5	1.2	40	0.5-1	0.3	0
1	100	1-4	2.5	80	1-3	1.5	50
2	100	2-4	3.0	100	0.5-3	1.7	70
4	100	1-4	3.4	70	1-3	1.6	100

*4 = Severe.

All the cholesterol-fed chickens, with the exception of a few which died early in the course of this experiment, had grossly fatty livers. The pulmonary arteries were examined in several animals from each group of cholesterol-fed birds, and in some, small, white and yellow, hard, raised nodules were seen. The incidence of these lesions was greater in the groups receiving the higher cholesterol rations. The pulmonary arteries were examined in nine control birds and no lesions were found.

3. *The Effect of Fifteen Weeks' Feeding a Cholesterol-Rich Diet:* The data are summarized in Table III and illustrated in Figs. 1 and 2. The mortality in this group was relatively high, and the results summarized in Table III have been arranged to show the average values (a) for the entire group and (b) for those birds which survived eleven and one-half weeks or more of cholesterol feeding. Again it was observed that there was a tendency for increased frequency and severity of lesions with the higher concentrations of cholesterol. However, when these groups are compared with the preceding groups fed the same percentage of cholesterol for only ten weeks, it is apparent that the frequency of occurrence of lesions and their severity tend to be less after fifteen weeks than

after ten weeks of cholesterol feeding. This tendency was more marked in the thoracic aorta than in the abdominal aorta.

TABLE III. EFFECT OF FIFTEEN WEEKS OF FEEDING OF CHOLESTEROL

CHOLESTEROL IN DIET (PER CENT)	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
Control	0	0	0	10	0.5	0.10	0
0.5	67	0.5-4	1.3	67	0.5-3	1.2	0
1	92	0.5-4	2.4	75	0.5-2	0.9	60
2	92	0.5-4	2.2	83	0.5-3	1.5	50
4	100	0.5-3	2.6	90	0.5-3	1.5	

*4 = Severe.

4. *The Effect of Duration of Cholesterol Feeding on Severity of Atheromatous Lesions:* We noted the occurrence of lesions after one and one-half to two weeks of feeding in one bird on a 1 per cent diet, in one on a 2 per cent diet, and in one on a 4 per cent cholesterol diet. These very early lesions were present in both the thoracic and abdominal aorta, and ranged in severity from slight to severe. In every case they were associated with the presence of a fatty liver.

TABLE IV. EFFECT OF DURATION OF FEEDING OF 0.5 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROMATOSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	25	0-0.5	0.1	0	0	0	
10	80	0.25-2	2.5	40	0.5-1	0.3	0
15	66	0.5-4	1.3	66	0.5-3	1.2	0

*4 = Severe.

The relationship of degree of atherosclerosis with the time factor is shown in Tables IV to VII and in Figs. 1 and 2. These tables are organized to compare the effect of a given per cent of cholesterol in the diet when given over the three periods of time, namely, five, ten, and fifteen weeks. The four tables show a marked increase in the frequency and severity of atherosclerosis of the thoracic and abdominal aorta when the cholesterol feeding period was increased from five to ten weeks. This is true for each concentration of cholesterol used. Furthermore, in each instance, although the fifteen-week results were significantly

higher than those of the five-week group, they were not as high as those recorded for the ten-week period of feeding, as previously mentioned. This relationship holds even when the birds which died early in the fifteen-week series are excluded from the tables. This phenomenon will be discussed later when the effects on blood cholesterol levels and body weights are considered.

TABLE V. EFFECT OF DURATION OF FEEDING OF 1 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	66	0.5-2	0.7	8	0-1	0.09	
10	100	1-4	2.5	80	1-3	1.5	50
15	92	0.5-4	2.4	75	0.5-2	0.9	60

*1 = Severe

TABLE VI. EFFECT OF DURATION OF FEEDING OF 2 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	75	0.5-2	1.3	33	0-2	0.4	
10	100	2-4	3.0	100	0.5-3	1.7	70†
15	92	0.5-4	2.2	83	0.5-3	1.5	60‡

*1 = Severe

†Eight birds examined.

‡Five birds examined.

TABLE VII. EFFECT OF DURATION OF FEEDING OF 4 PER CENT CHOLESTEROL ON THE DEVELOPMENT OF ATHEROSCLEROSIS

WEEKS FED	THORACIC AORTA			ABDOMINAL AORTA			PULMONARY ARTERY
	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)	DEGREE OF ATHERO- SCLEROSIS	AVERAGE GRADE*	BIRDS WITH LESIONS (PER CENT)
5	100	0.5-4	1.9	33	0.5-2	0.5	
10	100	1-4	3.4	70	1-3	1.6	100†
15	100	0.5-3	2.6	90	0.5-3	1.5	

*4 = Severe.

†Three birds examined.

An examination of these tables shows that, in general, atherosclerotic lesions in the abdominal aorta tended to occur somewhat later than those in the thoracic aorta and were less advanced. There was also a fair degree of correlation, by and large, between the severity of the lesions in the two portions of the aorta, although there were individual cases in which relatively severe lesions occurred in one portion of the aorta in the absence of any lesions in the other portion.

B. Observations on the Blood Cholesterol Levels.—

The data are summarized in Fig. 3. Blood cholesterol levels on the control birds varied within moderate limits throughout the experimental period, the

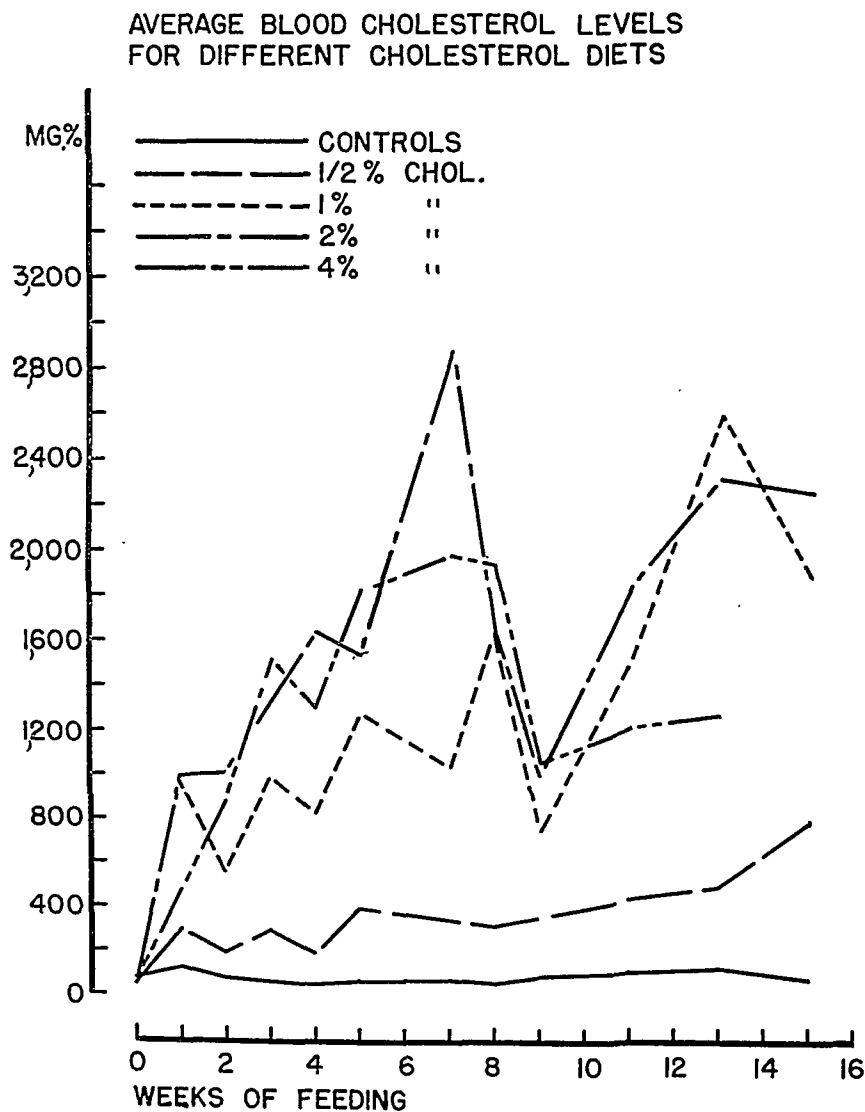


Fig. 3.

highest and lowest average readings for any week being 65 and 159 mg. per cent, respectively, and the average being 95 mg. per cent. The control values for *all* the birds in this study ranged from 34 to 108 and averaged 74 mg. per cent. The highest individual blood cholesterol recorded for any control bird was 274 mg.

per cent. This was definitely the exception, as the usual individual level was in the neighborhood of 80 mg. per cent. The blood cholesterol levels of the control birds varied from week to week but did not show any consistent trend with increasing age of the birds.

The chickens which received cholesterol all showed an immediate and marked increase in blood cholesterol after one week of feeding. This rise amounted to from six to twelve times the original levels. The smallest immediate increase was in the group receiving 0.5 per cent cholesterol, and amounted to a sixfold increase, from 51 to 312 mg. per cent. The greatest increase was in the 2 per cent group, which rose from an initial average of 81 to 1,003 mg. per cent in the course of one week. The 1 per cent group rose from 60 to 968 mg. per cent and the 4 per cent group from 96 to 471 mg. per cent.

During subsequent weeks, the 0.5 per cent cholesterol groups showed only a slight tendency to a further rise in blood cholesterol with continued feeding of cholesterol. There was a gradual rise to a maximum average value of 772 mg. per cent at the fifteenth week. The 1 per cent group showed an upward trend for the fifteen-week period. The maximum average value recorded in this group was 2,580 mg. per cent. There was a sharp dip to 769 mg. per cent at the ninth week, for which we have no explanation.

The 2 per cent group showed a steep rise in blood cholesterol levels to a high average value of 2,882 mg. per cent at the seventh week. Thereafter there was a marked decline to 1,003 mg. per cent on the ninth week and a secondary rise to 2,258 mg. per cent by the fifteenth week. By drawing a curve between the points (Fig. 3) it can be seen that the curve so obtained has a steep initial slope and then flattens out. This phenomenon was also observed in the group being fed 4 per cent cholesterol.

The 4 per cent group rose rapidly to a value of 1,540 mg. per cent by the third week, and then began a steady decline to 1,053 mg. per cent at the ninth week. The curve for this group shows a steep initial slope, a plateau, and then a fall. The correlation of this phenomenon with the data on weight and food intake is of interest in probing the reasons for this phenomenon and is discussed below.

The observations on blood cholesterol may be summarized as follows:

1. Feeding of cholesterol in dosages varying from 0.5 per cent to 4 per cent produced a marked rise in the blood cholesterol of from six- to twelvefold within the space of one week.
2. Feeding 1 per cent, 2 per cent, and 4 per cent cholesterol in the diet produced a sustained lipemia considerably greater than that produced by feeding 0.5 per cent cholesterol.
3. Diets containing 2 per cent and 4 per cent cholesterol resulted in a hypercholesterolemia which tended to decline toward the end of the fifteen-week period, whereas that produced by 1 per cent cholesterol showed a steady upward trend.
4. Diets containing cholesterol in excess of 0.5 per cent result in a lipemia which is marked, but not parallel to the further increases in the concentration of cholesterol in the diet. Thus, 2 per cent and 4 per cent of cholesterol produced about the same degree of lipemia as 1 per cent.

and that the coronary arteries are normal. The theoretical question, what degree of dilatation without hypertrophy may be reached by myocardium?, is answered by this heart more effectively than by any known experimental technique, or by any other clinical observation.

Illustrations as well as the specimen, which at first glance resembles a distended ovarian cyst, will be shown.

THE DIFFERENT TYPES OF INTRAVENTRICULAR BLOCK.—MARCEL SEGERS, M.D., BRUSSELS, BELGIUM.

Published in full, *Am. Heart J.* 37:92, 1949.

COARCTATION OF THE AORTA.—MORSE J. SHAPIRO, M.D., MINNEAPOLIS, MINN.

The subject of coarctation of the aorta has assumed practical significance now that this abnormality can be cured by surgical intervention. It seemed important, therefore, to examine the data on twenty patients observed over a period of several years. From this study the following information has been obtained:

1. The diagnosis is frequently missed.
2. Follow-up studies revealed a gradual increase in blood pressure with an accompanying increase in size of the left ventricle. The extent of erosion of the ribs, where this sign is present, increases.
3. Erosion of the ribs is not always present.
4. There is no clear correlation between rib erosion, size of the left ventricle, and degree of constriction of the aorta.
5. Collateral circulation does not develop if an accompanying patent ductus arteriosus of good size is present.
6. Enlargement of the left subclavian artery, as revealed by x-ray films, is frequently a helpful diagnostic sign.
7. Four cases observed during surgical intervention and three at post-mortem examination will be discussed in detail.

BIOLOGIC STANDARDIZATION OF DIGITALIS PRODUCTS BY MEANS OF THE GUINEA PIG METHOD: COMPARISON WITH THE CAT METHOD; DIFFERENCES AND ADVANTAGES.—EUGENIO D. DA SILVA CARMO, M.D., RIO DO JANEIRO, D.F., BRAZIL.

Abstract in English not available.

MOVEMENTS AND SOUNDS OF THE HEART VALVES OF VARIOUS LABORATORY ANIMALS (MOTION PICTURE WITH SOUND RECORDINGS).—H. L. SMITH, M.D., E. J. BALDES, M.D., AND HIRAM E. ESSEX, M.D., ROCHESTER, MINN.

The hearts of various laboratory animals were perfused with oxygenated Ringer-Locke solution and were kept beating for various periods of time. Openings were made in the different chambers of the hearts and motion pictures were made of the movements of the mitral, tricuspid, aortic, and pulmonic valves. Sound recordings and electrocardiographic tracings were made at the same time.

X-RAY KYMOGRAPHY IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS.—K. SHIRLEY SMITH, M.D., AND FRANKLIN G. WOOD, M.D., LONDON, ENGLAND.

In the present study x-ray kymography has been applied to the diagnosis of patent ductus arteriosus. It is considered that the radiokymographic appearances which we now present are characteristic and diagnostic of this congenital abnormality.

cholesterol content of the diet. The failure to gain in weight may therefore be due in part to a decline in food intake, the reasons for which are not apparent. We cannot exclude impaired intestinal absorption or even some faulty endocrine or metabolic mechanism.

DISCUSSION

Our results show clearly that in the chicken, at least, there is a direct relationship between the concentration of cholesterol in the diet and the frequency of occurrence and severity of atherosclerotic lesions which develop as a result of the feeding of cholesterol. There is also a direct relationship between the duration of the feeding period and the frequency of occurrence and severity of atheroma, at least for the first ten weeks of feeding. Thereafter, both frequency and severity of atheromatosis tend to decline. The reason for the lesser severity of the atherosclerosis after ten weeks of feeding is not clear. The decline in the blood cholesterol levels and the failure to gain in weight are correlative phenomena, but need not be the cause of the decreased severity of the atheromatosis. It is conceivable that only those animals with a superior ability to "tolerate" cholesterol survive beyond 10 weeks of feeding and hence the degree of atherosclerosis which they manifest is less.

There appears to be a correlation between the blood cholesterol levels and the degree of atheromatosis. This is most apparent in the five-week group, where there is a high degree of correlation. When ten weeks elapsed the frequency of occurrence of lesions for the 1 per cent, 2 per cent, and 4 per cent cholesterol-fed groups was about equal. This appeared to depend on the fact that the blood cholesterol levels of these groups were roughly similar. While the frequency of occurrence of lesions in all groups receiving over 0.5 per cent concentration of dietary cholesterol was roughly the same, the severity of the lesions was greater in the groups receiving the higher concentrations of cholesterol. This would indicate that the circulating blood cholesterol level is only a rough index to the progress of the atherosclerogenic process. The time factor, however, cannot be neglected, since the continued feeding of 0.5 per cent cholesterol resulted in a steady increase in the number of animals with atheroma. This was associated with a rise in blood cholesterol level.

The feeding of cholesterol in amounts exceeding 0.5 per cent of the diet does not cause a continuous progressive rise in the blood cholesterol levels. After a few weeks a plateau is reached. This probably indicates that there is an upper threshold to the amount of cholesterol which the chicken can ingest, assimilate, and distribute from the gastrointestinal tract and that amounts in excess are probably excreted unchanged in the feces.

There can be no doubt that cholesterol feeding profoundly affects the appetite and well-being of the experimental animals. They are small, fail to gain in weight, lose their feathers, and in many instances become sick and die. The remarkably fatty livers which are found in all birds on high-cholesterol diets no doubt contribute considerably to this phenomenon.

Microscopic studies reveal that there is no essential difference between the vascular lesions seen in the chicken as a result of cholesterol feeding and those seen in atherosclerosis in man. Further, vascular lesions occur in the chicken in many organs. We have observed atherosclerotic lesions of all grades of severity in the aorta, heart valves, coronary arteries, and pulmonary arteries of the chicken. Similar lesions have also been found in the blood vessels of the spleen, adrenal and thyroid glands, and in the main renal arteries.

Careful histologic examination of sections of brain and kidney failed to reveal any atheromatosis of the renal arterioles or brain vessels.

Details of the histologic appearance of the vascular lesions have been described previously by Dauber and Katz.³ We also found atheroma of the pulmonary arteries and of large veins, lesions which were not reported by them.

We wish to call attention to the occurrence of gross atheroma in our chickens after two weeks of feeding. To our knowledge this constitutes the shortest period of time for which cholesterol must be fed in order to obtain lesions. It takes thirty to forty-five days to produce microscopic atheroma and fifty-five to seventy-eight days to produce gross lesions in the rabbit.⁵ Dauber and Katz^{2,3} reported that the earliest intimal changes they observed in the chicken occurred at forty-two days of feeding, and the earliest gross lesions at forty-nine days.

It would appear, therefore, that atherosclerosis can be produced in the chick with as great, or greater, ease and rapidity than in the rabbit.

SUMMARY

1. The chicken, a member of the class *Aves*, possesses distinct advantages as an experimental animal in the study of atherosclerosis.

2. Feeding of cholesterol in concentrations of 0.5 per cent, 1 per cent, 2 per cent, and 4 per cent of the diet for periods of five, ten, and fifteen weeks was investigated.

3. There was a direct relationship between the concentration of cholesterol in the diet and the frequency and severity of the atherosclerosis which resulted.

4. There was a relationship between the duration of the feeding period and the degree of atherosclerosis produced for each concentration of cholesterol in the diet.

5. With concentration of cholesterol in the diet above 0.5 per cent, increasing the feeding period beyond ten weeks did not appear to lead to any increase in the amount of atherosclerosis.

6. Atherosclerosis occurred as early as two weeks after the commencement of feeding in our birds. The early occurrence of atherosclerosis in the chicken is related to the enormous increase in blood cholesterol which occurs during the first week of cholesterol feeding.

7. Amounts of cholesterol in excess of 0.5 per cent produce much the same degree of hypercholesterolemia, suggesting that there is an upper threshold for the assimilation of cholesterol.

8. There is a semidirect relationship between the degree of lipemia and the degree of atherosclerosis which is found.

9. A method for the consistent production of atherosclerosis in the chicken has been standardized for (a) varying concentrations of cholesterol in the diet, and (b) time course of feeding.

We are grateful to the following technicians and assistants for their help in carrying out these studies: Mrs. L. Havel (D. V. Dauber Memorial Research Assistant), Miss Marilyn Dudley, Miss Lorraine Adams and Mr. Grady Crowley. We are indebted to Dr. S. Rodbard for his valuable suggestions.

REFERENCES

1. (a) Fox, H.: *In*: Cowdry, E. V.: Arteriosclerosis, New York, 1933, the Macmillan Company, p. 153.
(b) Fox, H.: Some Comments on Arteriosclerosis in Wild Mammals and Birds, *Bull. New York Acad. Med.* 15:748, 1939.
(c) Yamagiwa, K., and Adachi, O.: *Verhandl. d. Japan pat. Gesellsch.* 4:55, 1914. (From Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick, *Arch. Path.* 34:937, 1942).
2. Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick, *Arch. Path.* 34:937, 1942.
3. Dauber, D. V., and Katz, L. N.: Experimental Atherosclerosis in the Chick, *Arch. Path.* 36:473, 1943.
4. Dauber, D. V.: Spontaneous Arteriosclerosis in the Chicken, *Arch. Path.* 38:46, 1944.
5. Anitschkow, N.: Das Wesen und die Entstehung der Atherosklerose, *Ergebn. d. inn. Med. u. Kinderh.* 28:1, 1925.
6. Paterson, C., Slinger, S. J., and Gartley, K. G.: Experimental Coronary Arteriosclerosis in Cockerels, Paper given at the meeting of The American Scientific Society, Nov. 2, 1947.
7. (a) Herrmann, G. R.: Blood and Tissue Chemical Studies in Fowl, *Proc. Soc. Exper. Biol. & Med.* 61:229, 1946.
(b) Herrmann, G. R.: Effect of Choline on Blood and Tissues With Especial Reference to Cholesterol in Old Hens, *Proc. Soc. Exper. Biol. & Med.* 61:302, 1946.
8. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, *J. Biol. Chem.* 106:745, 1934.

THE CAUSE AND EFFECTS OF FLOW THROUGH DEFECTS OF THE ATRIAL SEPTUM

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ALTHOUGH it has long been known that the direction of flow through large defects of the atrial septum is from left to right, the reason for the direction of the shunt has received but little consideration until recently. According to White,¹ it seems generally to have been assumed that the left-to-right flow is due to higher pressure in the left atrium—this in spite of the fact that in experimental animals mean pressures in the two atria are approximately equal,² and in the absence of evidence to suggest that the situation in this regard is different in man.

In 1942 Uhley³ proposed an attractive and logical theory which attributed the direction of the shunt to an effect of gravity, related to the cephalad location of the left atrium with respect to its fellow of the right side. Brannon, Weens, and Warren,⁴ however, later reported that in two cases of atrial septum defect the oxygen content of blood obtained from the right atrium remained higher than that of vena caval blood during recumbency and in the head-down position, a finding which indicates that flow continued from left to right after the gravity effect had been eliminated or reversed.

More recently Stead and Warren⁵ stated that the persistent left-to-right flow demonstrates that in cases of atrial septum defect pressure in the left atrium is higher than that in the right, and commented upon the seemingly paradoxical corollary that the right ventricle fills to a greater degree than the left ventricle, although right atrial pressure is less than pressure in the left atrium. They concluded that the reason for the large output of the right ventricle in this anomaly has not been determined.

Almost certainly, however, the reason for the left-to-right shunt (and the associated increase in right ventricular output) is to be found in the factors which determine the direction and the magnitude of flow through other apertures connecting adjacent chambers or vessels of the cardiovascular system such as ventricular septal defect, patent ductus arteriosus, and arteriovenous fistula.

THE DETERMINANTS OF FLOW BETWEEN ADJACENT COMMUNICATING VESSELS OR CAVITIES

The direction of flow through an ostium connecting adjacent vessels (or adjacent chambers of the heart) is determined by the magnitude of the resistance which, at the site of the communication, opposes the movement of blood into the

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natural channels pertaining to each of the communicating cavities: if the resistance opposing "natural" flow is unequal in the two vessels or chambers, blood will flow from the one in which resistance is greater into the other in which resistance is less.

The resistance to natural flow in each vessel depends upon the rate of flow into the vessel, its size in the region of the communication, and the anatomic features of the structures into which it normally leads. Resistance varies directly with the square of the velocity of flow, and inversely with the size of the vessel; with regard to the features of the structures into which the vessel leads, resistance is in general directly proportional to the length of these structures and inversely proportional to their cross-section areas.

Since pressure is a quantitative manifestation of resistance, it follows that the direction of flow through the communication is from the cavity in which pressure is higher into the adjacent cavity in which pressure is lower. However, if the ostium is of great size, a relatively large quantity of blood may be diverted through it even though the difference between the pressures on either side of the ostium is very small.

ATRIAL PRESSURES AND THE NORMAL RESISTANCES TO ATRIOVENTRICULAR FLOW

Rates of Atrial Inflow and Outflow.—In the normal subject the quantities of blood which enter and leave the right and left atria are necessarily equal over any considerable period of time. Inflow occurs continuously, but outflow is suspended during the period of ventricular systole. Flow into the ventricles is most rapid early in ventricular diastole, immediately after the opening of the atrioventricular valves.

Size of the Atria.—In the cadaver the right atrium of normal hearts is somewhat larger than the left,⁶ but it is likely that the difference in their volumes is related to agonal and post-mortem accumulation of blood in the right side of the heart. During life the capacities of the two atria are probably about equal. Both atria and the great veins leading into them are readily distensible. The walls of the left atrium are one and one-half times as thick as those of the right.⁶

The Natural Channels of Atrial Outflow.—Each atrium leads via its atrioventricular opening, over the open atrioventricular valve into the cavity of its pertaining ventricle.

The right A-V opening is considerably larger than the corresponding orifice on the left side, "being sufficient to admit the ends of four fingers," while the mitral orifice admits "only two fingers"⁶ (Fig. 1). The average circumference of the normal tricuspid orifice is one-fourth to one-third greater than that of the mitral opening,⁷ and its cross area about 50 to 75 per cent greater. Therefore, the mitral orifice must offer more resistance to the passage of blood than does the tricuspid orifice.

Similarly, the inflow tract of the left ventricle is longer and narrower than that of the right ventricle; on the whole, the left ventricle is longer, and in cross section smaller, than the corresponding chamber of the right side⁶ (Fig. 2).

These factors tend to produce greater resistance to the movement of blood toward the apex on the left side of the heart. It is also possible that the thicker walls of the left ventricle are more resistant to stretching than are the thinner walls of the right ventricle, so that near the end of diastole the resistance to filling may be greater on the left side. In addition, the tricuspid valve is more delicately constructed than the mitral valve, whose cusps are thicker and larger.⁶ Because of this it is possible that the tricuspid valve opens more readily at the end of the postsphygmic period. Further, it is likely that during the period of rapid filling the three cusps of the more efficient valve of the right side lie in closer proximity to the walls of the ventricle than do the two cusps of the less efficient mitral valve, and hence impinge less upon the cavity of the inflow tract (Fig. 1).

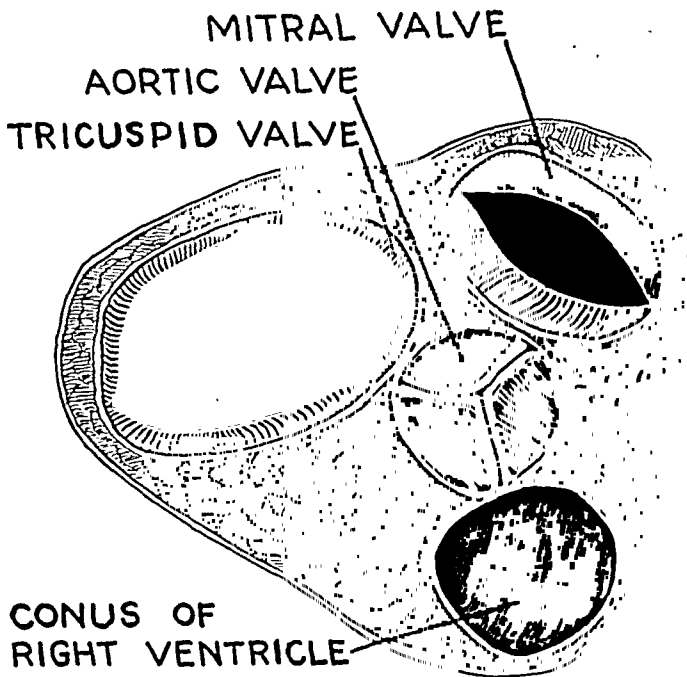


Fig. 1.—Schematic representation of the atrioventricular orifices and open atrioventricular valves, seen from above.

Atrial Pressures.—It appears, thus, that the resistance which normally opposes flow into the atria during ventricular systole is of about the same magnitude on the two sides, but that the resistance to atrioventricular flow is greater on the left side. It naturally follows that in normal subjects pressure in the two atria should be about equal during ventricular systole, but that during ventricular diastole pressure in the left atrium should exceed that in the right atrium.

This difference, however, is probably of small magnitude, for two reasons: First, both A-V orifices are of large size (the right roughly 10.5 square cm., the left 7.0), and both ventricles are almost empty of blood at the beginning of diastole.⁸ The resistance opposing atrioventricular flow is then very slight on both sides, and the absolute difference as expressed by higher pressure in the left

atrium could hardly be very great. Second, the tendency toward the development of slightly higher pressure in the left atrium is probably counterbalanced by increase in the size of the readily distensible left atrium and pulmonary veins, so that pressure in the left atrium actually may exceed right atrial pressure only momentarily—at the beginning of the period of rapid ventricular filling and again during the brief period of atrial systole. The left atrium, slightly more distended than the right (and relatively hypertrophied) probably contracts with greater vigor, causing left atrial pressure momentarily to exceed pressure in the right atrium at this time.

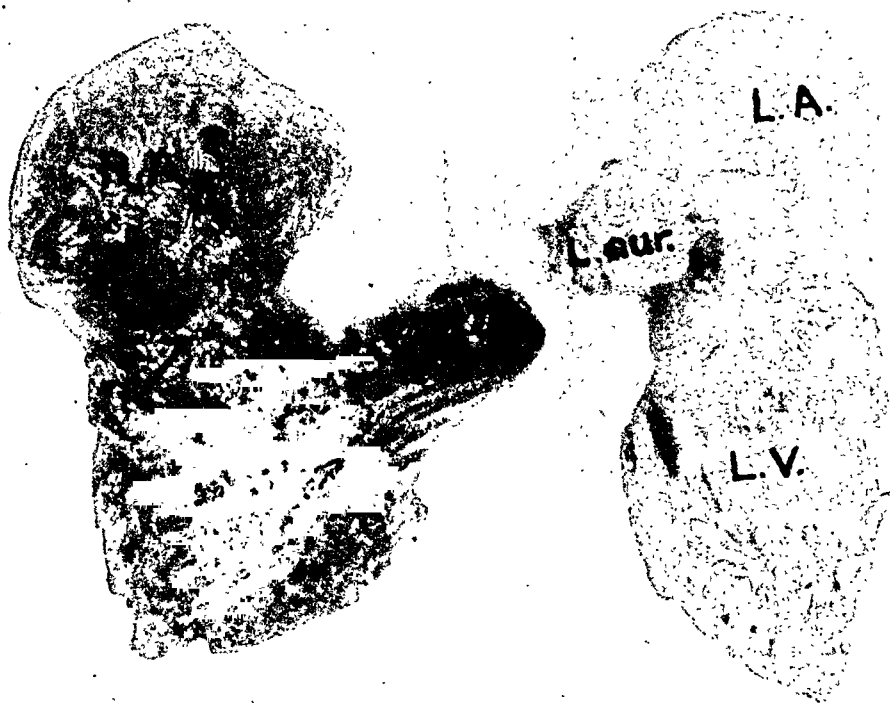


Fig. 2.—Casts of the cavities of a normal heart, viewed from their antiseptal surfaces. *R.A.*, right atrium; *R.V.*, right ventricle; *P.A.*, pulmonary artery; *L.A.*, left atrium; *L.V.*, left ventricle; *L. aur.*, left auricle.

FLOW THROUGH DEFECTS OF THE ATRIAL SEPTUM

It seems certain that in most typical clinical cases the cardiovascular system was normal at birth except for the defect of the atrial septum, and that the other anatomic abnormalities result from the diversion of blood through the abnormal aperture. The hearts of normal infants (Fig. 3) possess anatomic features similar to those of adults, and it is likely that the tendency toward higher pressure in the left atrium appears shortly after the onset of respiration and functional closure of the ductus arteriosus; indeed, this tendency probably produces and

maintains functional closure of the foramen ovale. It is likely, therefore, that the factors concerned with flow through the septal defect begin to operate at an early age.

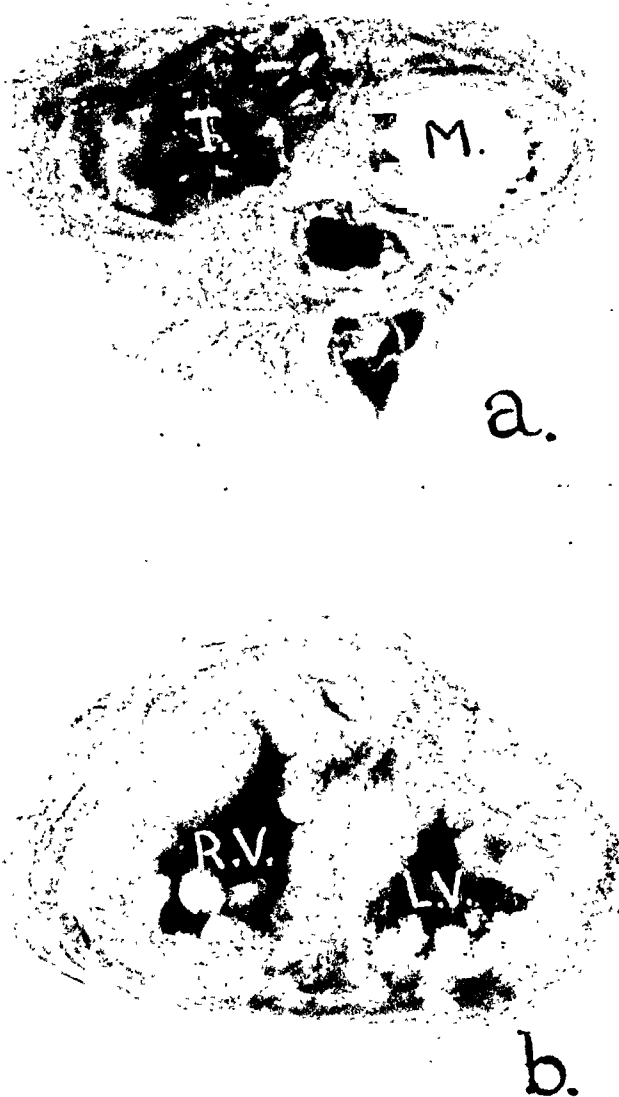


Fig. 3.—*a*, Cross section of the normal heart of a stillborn infant at term, in the same plane as that of Fig. 1. *T*, tricuspid orifice; *M*, mitral orifice. *b*, Section of same heart at a level 1.0 cm. below the atrioventricular orifices. *R.V.*, right ventricle; *L.V.*, left ventricle.

Direction of Flow.—In the beginning, when the tendency toward higher pressure in the left atrium initially appears, it would seem that little or no blood should flow through the defect during ventricular systole. During this period the atria are serving merely as readily distensible reservoirs, both of them capable of receiving considerable quantities of blood with only very slight increase of pressure, and each of them receiving the same amount of blood from the great veins which empty into it.

At the end of the postsphygmic period, as the A-V valves snap open and the period of rapid ventricular filling ensues, the anatomic factors concerned with resistance to atrial outflow come suddenly into play, and the resistance opposing flow into the natural outlet, the ventricle, becomes greater on the left side than on the right. Therefore, as blood begins rapidly to move out of the atria, a portion of the outflow from the left atrium is diverted through the septal defect into the right atrium; the normal tendency toward the attainment of higher pressure in the left atrium is counterbalanced by the shunting of blood into the right atrium, rather than by distention of the left atrium and its tributary veins. Blood continues to move through the interatrial communication until the resistances to atrioventricular flow have been equalized on the two sides, or until closure of the A-V valves with the onset of ventricular systole.

Early Dynamic Effects of the Shunt.—It is obvious that from the first a balance must be established whereby under any stable set of circumstances the output of each ventricle remains constant from beat to beat, and that so long as the heart remains competent the output of the left ventricle and, in turn, the rate of flow from the venae cavae into the right atrium will be maintained at normal rates. Since the blood shunted into the right atrium through the septal aperture is added to the normal caval inflow, it is clear that right atrial flow, right ventricular filling and output, and, in turn, pulmonary flow and the rate of flow into the left atrium are increased above the normal by the amount of blood which moves through the septal aperture.

In the beginning, as has been noted, there is no tendency for blood to flow through the defect during ventricular systole. However, once the shunting during ventricular diastole has begun, there is consequent increase of flow into the left atrium, which per se would cause this chamber to fill more rapidly during ventricular systole than its fellow. It is likely, therefore, that from the first, left-to-right flow through the defect occurs during both phases of the ventricular cycle, and, indeed, that the greater portion of the shunting occurs during ventricular systole, when the rate of caval flow into the right atrium is normal, but the rate of flow into the left atrium is increased.

Anatomic and Later Dynamic Effects.—The mean rates of flow through the two atria are equal, increased above the normal by the amount of blood which flows through the septal defect. However, outflow from the left atrium is divided into atrioventricular and interatrial portions, while the right atrium has only one channel of egress, the right ventricle. Moreover, blood flows out of the left atrium during both phases of the ventricular cycle, while outflow from the right atrium is suspended during ventricular systole. For these reasons, the average quantity of blood contained within the right atrium exceeds that contained within the left atrium, the difference in their contents being most marked near the end of ventricular systole; during each complete cardiac cycle the mean quantity of blood contained by the left atrium is only slightly above normal, while the amount contained by the right atrium is increased in proportion to the quantity of blood shunted through the septal opening. Therefore, the thin walls of the right atrium are subjected to abnormal stretching, while the left atrium is, on the average, no more than normally distended with blood; consequently, the right

atrium tends gradually to dilate more and more, while the cavity of the left atrium remains approximately normal in size.

As dilatation of the right atrium gradually progresses and comes to exceed physiologic limits, the increasing capacity of this chamber tends to reduce resistance to inflow, so that with the passage of time the quantity of blood shunted through the defect gradually increases, this increase in turn causing further dilatation of the right atrium. Thus, over the years gradual augmentation of right ventricular filling and output occurs, and the work of this chamber continues progressively to be increased.

Atrial Pressures.—Because of the ready distensibility of the atria and the subatmospheric pressure within the thorax, and because of the very slight resistance opposing the filling of competent ventricles, the atria are capable of receiving and transmitting quantities of blood greatly in excess of their usual quotas without increase of intra-atrial pressures. During strenuous exercise, for example, the stroke volume of the normal heart may be trebled and the minute output increased sixfold without increase of right atrial pressure.⁹ It would not be expected, therefore, that atrial pressures should be altered significantly in cases of atrial septum defect, despite the fact that the quantity of blood entering each of the atria is considerably or markedly increased. Mean pressure in the right atrium and the form of the right atrial pressure curve have indeed been found to be normal (in the absence of congestive heart failure) in cases studied by us and by others.^{4,10,12}

The existence of normal pressure in the right atrium in no way precludes increased filling of the right ventricle in cases of atrial septum defect. Atrial or "filling" pressure has nothing to do with the filling of a competent ventricle; the amount of ventricular filling and the size of the stroke volume are determined only by the quantity of blood contained in the appertaining atrium at the beginning of ventricular diastole, the quantity which flows into the atrium during the whole of this period, and to a minor degree by the power of atrial contraction. The lack of correlation between atrial pressure and ventricular filling does not necessarily indicate, as Stead and Warren⁵ have suggested, that the ventricle dilates actively in order to receive more blood and thus to increase its output; but, rather, testifies to the very slight resistance opposing passive filling of competent ventricles, which allows maximal filling and output without elevation of atrial pressures above the levels recorded under basal conditions. Only when the ventricle has become incompetent, and the amount of its residual blood considerably increased, does the resistance opposing ventricular filling increase sufficiently to cause elevation of atrial pressure.

Indeed, it seems probable that right atrial pressure may not exceed normal limits in cases of atrial septal defect, even if the compensating right ventricle fails to cope adequately with the augmented venous return incident to muscular activity. During exercise the circulation rate increases without change of the balance between pulmonary and systemic flow so long as the right ventricle remains competent; right ventricular output, the quantity of blood diverted through the septal opening, and left ventricular output, increase in the same

proportion. However, as compensation of the right ventricle fails, the balance is temporarily disturbed: residual blood in the right ventricle increases, its output falls off, and right atrial pressure is increased because of the accumulation of blood in this chamber.

But consequent to the reduction of right ventricular output, filling of the left atrium is diminished, with a resultant tendency toward decline of left atrial pressure. The resistance opposing left-to-right flow through the shunt is therefore increased in relation to the resistance offered to flow into the right ventricle, and the magnitude of the interatrial shunt is thereby reduced. Total flow into the right atrium then decreases, right atrial pressure declines, and the burden of the right ventricle is lessened so that its output may now keep pace with the rate of its filling; compensation is restored because the decrease in the magnitude of the shunt exceeds the reduction in the output of the failing ventricle. Although the fraction of left atrial outflow which enters the left ventricle increases as the right ventricle fails, it appears that in many cases the absolute quantity of blood entering the left ventricle (and consequently the output of this chamber and the rate of systemic flow) is subnormal under conditions of usual daily activity, as attested by the frequent finding of a hypoplastic aorta.¹¹

By this unique train of events, incipient cardiac decompensation promptly results in decrease of the heart's burden without abnormal elevation of venous pressure, and with relatively slight reduction in the blood supplied to the tissues of the body. The frequent absence of symptoms in the presence of pronounced physical signs, the active, useful lives which many of these persons have led, and the not uncommon attainment of ripe old age¹¹ may thus be explained.

Whether left atrial pressure actually remains normal or near normal in cases of defect of the atrial septum is, of course, not known, for pressure has never been measured in this chamber of the normal human heart; even in experimental animals accurate estimation of left atrial pressure is difficult because of artifacts produced by movements of the heart and other factors. The fact that dilatation of the left atrium fails to occur, even in cases of Lutembacher's syndrome, is, however, strong indirect evidence against great increase of left atrial pressure.

In several cases studied by venous catheterization the catheter entered the left atrium via the septal defect, so that it was possible to obtain recordings or readings of pressures in this cavity. In Brannon, Weens, and Warren's⁴ case it appeared that pressure in the left atrium was somewhat higher than that in the right, but the pressure recording from the left atrium was distorted by large artifactual oscillations. In the case studied by Dexter and associates,¹⁰ mean pressure in the left atrium seemed to exceed right atrial pressure by 4.0 mm. of mercury. In three cases recently reported by Cournand and associates,¹² mean pressure was higher in the left atrium by 4.0, 1.6, and 2.5 mm. Hg, respectively, and the fluctuations of the manometer were of much greater amplitude when the tip of the catheter was in this chamber.

Whether the pronounced fluctuations recorded in Cournand's cases (about 22 mm. Hg between maximal and minimal pressures during a single cardiac cycle in one case) accurately express actual changes of left atrial pressure is, however,

uncertain. They may have resulted in part from artifactual, local changes of pressure related to movements of the catheter tip as currents of blood impinged against it or as the heart moved or the atrium contracted, or related to the "velocity head"⁹ of currents directed toward or away from its aperture. The very magnitude of the fluctuations—exceeding the amplitude of the pressure pulse in the pulmonary artery of normal individuals (12 to 20 mm. Hg), and almost equaling the pulmonary artery pulse pressure in one of Dexter's¹⁰ cases of atrial septum defect (25 mm. Hg), in which the interatrial shunt was estimated as 65 per cent of left atrial inflow—suggests the possibility of artifactual influences. Further, it is difficult to understand why, in the presence of free interatrial communication, such sharp changes in left atrial pressure should fail to affect the form of the right atrial pressure curve, especially during systole of the atria, at a time when the volume of the contracting right atrium is decreasing, its walls are maximally resistant to distention, and the resistance to atrioventricular flow is greatest.

Cournand and his associates¹² suggest that in normal man the pressure relationships between the two atrial cavities may be similar to the curves recorded in their cases of atrial septum defect, and attribute the differences in mean and instantaneous pressures to three factors: lesser distensibility of the thicker-walled left atrium, smaller capacity of the venous reservoir of the lesser circulation, and more pronounced effects of ventricular activity upon volume and tension in the left atrium than in the right. They suggest also that the same factors are responsible for the shunting of blood through defects of the atrial septum.

The opinion that normal differences between pressures in the right and left atria are due primarily to differences in the anatomic features of the two sides of the heart, and that the same factors are responsible for flow through defects of the atrial septum, is in accord with the general concept presented in this paper. It is doubtful, however, that the factors suggested by Cournand and associates are of prime importance in atrial pressure relationships. There is no reason to believe that within limits hypertrophied muscle fibers resist stretching more than nonhypertrophied fibers, and therefore it is unlikely that the left atrium offers appreciably greater resistance to inflow than does its fellow, except perhaps momentarily at the end of the phase of rapid atrial filling. The effective, intrathoracic reservoir of the caval system is hardly more capacious than the pulmonary venous system, although the four pulmonary veins, because of their relatively small individual calibers, may afford less protection than the larger venae cavae against factors (such as atrial contraction) which tend to cause abrupt increase of atrial pressure. The thicker, firmer cusps of the mitral valve⁶ and the larger, stronger papillary muscles inserted into its chordae tendinae should serve to mitigate the effects of the powerful contraction of the left ventricle upon volume of, and pressure in, the left atrium.

Pulmonary Arterial Pressure.—The increase in the rate of blood flow through the lungs tends of itself to cause elevation of mean pressure in the pulmonary arteries; per se, an interatrial shunt amounting to half of the left atrial inflow, with consequent doubling of the right ventricular output, would result in a fourfold increase of mean pulmonary arterial pressure. The tendency toward the develop-

ment of such marked hypertension is opposed by the existence of the septal defect itself, which acts to reduce the total resistance of the lesser circulation, and is in part counterbalanced by progressive dilatation of the pulmonary arteries, which has a similar effect upon resistance—directly, because of the increased size of the vessels, and indirectly, because of the resultant diminution in the linear velocity of flow. These mitigating factors cannot be expected to prevent, over the years, gradual and progressive elevation of mean pulmonary arterial pressure to definitely hypertensive levels. As in other instances in which mean arterial pressure is elevated because of increase in ventricular stroke volume,⁹ there occurs relatively great elevation of the systolic pressure and much less pronounced rise of the diastolic. Pulse pressure is consequently increased, and the pulse wave rises and falls more quickly than is normal; these features of the pulse wave account for the throbbing of the pulmonary arteries observed fluoroscopically in clinical cases—the characteristic “hilar dance.”

It is to be noted that although in proportion to the increase of mean pressure the rise of diastolic pressure is of relatively small magnitude, diastolic pressure is necessarily increased above normal or usual levels unless there is only slight elevation of mean pressure. Thus, it is not necessary to assume the existence of increased “peripheral resistance” in the pulmonary circuit in order to explain the occurrence of slight or moderate elevation of the pulmonary diastolic pressure. All the features of the pulmonary hypertension observed in cases of atrial septal defect^{4,10} are adequately explained as effects of an augmented output of the right ventricle, provided allowance is made for the relatively wide ranges of pulmonary arterial pressures recorded in normal subjects by techniques employing cardiac catheterization. If the shunt is of considerable magnitude, one should expect definite but not marked elevation of mean pressure in the pulmonary arteries, great increase of pulse pressure, striking elevation of systolic pressure, and slight or moderate elevation of diastolic pressure.

SUMMARY

The reason for the shunting of blood from left to right through large defects of the atrial septum has been sought in a consideration of the factors which determine the direction of flow through other abnormal apertures connecting adjacent vessels or adjacent cavities of the heart. This consideration leads to the conclusion that the direction of the interatrial shunt is due to differences in the normal anatomic features of the atrioventricular orifices and the ventricles of the right and left sides of the heart.

The mitral orifice is the smaller, the tricuspid the larger of the two atrioventricular openings. The cavity of the left ventricle is longer and narrower than that of the right ventricle, which is shorter and in cross section larger than its fellow. These differences (and perhaps also the thicker walls of the left ventricle and the less efficient operation of the mitral valve as compared with that of the tricuspid valve) are responsible for greater resistance to the flow of blood from atrium into ventricle on the left side of the heart, with a consequent tendency toward the attainment of higher pressure in the left atrium than in the right

atrium during the period of ventricular diastole. Although this tendency is in large part counterbalanced in normal subjects by distention of the left atrium and pulmonary veins, it is considered sufficient to initiate the movement of blood from the left atrium into the right through a large defect of the atrial septum.

Once the interatrial shunt is initiated, a train of effects naturally ensues whereby flow through the defect occurs during both phases of the ventricular cycle and gradually increases in amount, and filling and output of the right ventricle are progressively augmented, with corresponding increase in the rate of pulmonary flow and consequent elevation of pulmonary arterial pressure. Progressive dilatation of the right atrium, dilatation and hypertrophy of the right ventricle, and dilatation of the pulmonary arterial tree develop along with the gradual increase in the magnitude of the shunt, but the left atrium escapes enlargement because of the additional channel of outflow provided by the septal defect.

Atrial pressures remain normal because of the ready distensibility of the atria and great veins, the negative intrathoracic pressure, and the very slight resistance which opposes the filling of competent ventricles. Even if the right ventricle fails to cope adequately with the augmented return incident to unusual or ordinary activity, it seems likely that resultant decrease in the relative magnitude of the interatrial shunt quickly limits the burden imposed upon the right ventricle and prevents abnormal elevation of right atrial and venous pressures.

REFERENCES

1. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Company.
2. Wiggers, C. J.: Observations on the "Effective" Pressure in the Right and Left Auricles, *Am. J. Physiol.* 33:13, 1914.
3. Uhley, M. H.: Lutembacher's Syndrome and a New Concept of the Dynamics of Interatrial Septal Defect, *AM. HEART J.* 24:315, 1942.
4. Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial Septal Defect: Study of Hemodynamics by the Technique of Right Heart Catheterization, *Am. J. M. Sc.* 210:480, 1945.
5. Stead, E. A., Jr., and Warren, J. V.: Cardiac Output in Man: An Analysis of the Mechanisms Varying the Cardiac Output Based on Recent Clinical Studies, *Arch. Int. Med.* 80:237, 1947.
6. Gray, H.: Anatomy, Descriptive and Surgical, ed. 17, New York, 1908, Lea & Febiger.
7. Boyd, W.: A Text-book of Pathology, ed. 4, Philadelphia, 1943, Lea & Febiger.
8. Nylin, G.: On the Amount of, and Changes in the Residual Blood of the Heart, *AM. HEART J.* 25:598, 1943.
9. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, 1945, Williams & Wilkins Company.
10. Dexter, L., Haynes, F. W., et al.: Studies of Congenital Heart Disease. II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, With Observations on the Oxygen Saturation and Source of Pulmonary Capillary Blood, *J. Clin. Investigation* 26:554, 1947.
III. Venous Catheterization As a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect, and Auricular Septal Defect, *J. Clin. Investigation* 26:561, 1947.
11. Abbott, M. E. S.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association, Inc.
12. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of Blood Pressure From the Left Auricle and the Pulmonary Veins in Human Subjects With Interauricular Septal Defect, *Am. J. Physiol.* 150:267, 1947.

PENICILLIN THERAPY OF CARDIOVASCULAR SYPHILIS

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THE use of penicillin in the treatment of cardiovascular syphilis followed the successful use of this antibiotic in other forms of syphilis. With its use the fear of damaging Jarisch-Herxheimer reactions arose promptly, and it was not long before a few warning notes appeared in the literature. Dolkart and Schwemlein¹ reported the necessity of discontinuing penicillin in two patients because of untoward reactions. A review of these two cases, however, reveals that one patient had rheumatic heart disease and experienced anginal episodes after receiving 20,000 units of penicillin. He had received one injection of 10,000 units on each of the preceding two days without untoward reaction. The second patient noted precordial pain on the fourth day of penicillin, after a total of 700,000 units had been administered. He had had previous bouts of precordial pain seven and six years earlier. The relationship of penicillin to these symptoms is not a clear one.

Moore² reported the death in heart failure of one patient four days after the onset of combined malaria and penicillin therapy. Autopsy revealed plaques of aortitis with large hemorrhages in each. Callaway and coauthors³ reported the probable rupture of an aortic cusp in one of their patients several weeks after the completion of penicillin therapy. The latter accident might have been due to a therapeutic paradox secondary to the healing of the syphilitic inflammation, but we agree with Tucker and Farmer⁴ that there is little evidence that the phenomena described were due to Herxheimer reactions.

Russek and coauthors,⁵ Hill,⁶ and Tucker and Farmer⁴ have reported on penicillin therapy in a total of forty-six patients with cardiovascular syphilis in whom no adverse reactions were noted. Our own observations are in accord with the reports of these authors.

In the experience of one of us (E. W. T.), no harmful Herxheimer reactions during the treatment of cardiovascular syphilis have been noted in the past twelve years. For this reason, perhaps, Herxheimer reactions were feared less than on other services^{2,7} where extreme caution has been urged in the treatment of patients with cardiovascular syphilis. Nevertheless, it was thought advisable, in patients who had not received previous antisyphilitic therapy, to start treatment with a preparation less rapidly spirocheticidal than penicillin. For

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Aided by grants from the National Institute of Health, United States Public Health Service.

Comment.—This patient is an exquisite thrombophilic who suffered two attacks of acute coronary thrombosis and recurrent thrombophlebitis with repeated pulmonary embolizations. Dicumarol and femoral vein ligation failed to control the thromboembolic complications. Immediately after the initial deposit of heparin/Pitkin menstruum, extension of the coronary artery thrombosis was obviated and the thromboembolic complications were controlled. The response to the curative heparin/Pitkin menstruum therapy was most gratifying and throughout the prophylactic program there were no further thrombotic incidents.

CASE 10.—M. R. B., a 43-year-old, obese white physician, was first admitted to the Jewish Hospital of Brooklyn on Nov. 25, 1944. Five months prior to this admission he had a thrombophlebitis of the right leg for which the right femoral vein was ligated. Two weeks before this admission he had an episode of hemoptysis with elevation of temperature which was diagnosed as pulmonary infarction. He was hospitalized when the chest pain, cough, and fever continued and he developed signs of pleural effusion in the left pleural cavity. During this hospital stay he developed migratory thrombophlebitis of the left lower extremity with a rise in temperature. With conservative therapy all symptoms and signs abated and he was permitted to go home. Three days before the present admission, April 4, 1947, the patient was seized with a most agonizing attack of substernal pain of several hours' duration. This was obviously due to an acute myocardial infarction which an electrocardiogram showed to be of the posterior wall variety. Two days later he developed temperature and experienced pain at the base of the left lung. This pain persisted to the day of admission, and in view of the corroborative physical findings, was attributed to pulmonary infarction. A short pleuropericardial friction rub was heard at the left border of the heart. The admission electrocardiogram substantiated the diagnosis of acute posterior wall infarction. Anticoagulation therapy was instituted at once and he received a total of 1,900 mg. of heparin in the Pitkin menstruum distributed over nine deposits given over a period of thirty-two days. Although the patient was an extreme thrombophilic, he was also a hyperreactor and obtained excellent heparin responses from relatively small doses (100 to 200 milligrams). The heart sounds, which originally were of only fair quality, improved. There were no further thromboembolic episodes and the patient was permitted out of bed less than four weeks after onset. He was placed on a prophylactic heparin program with satisfactory results to date.

Comment.—This obese thrombophilic, who had recurrent attacks of thromboembolic disease despite vein ligation, suffered a third attack of acute coronary artery thrombosis. He was a heparin hyperreactor and maintained satisfactory anticoagulation effects with modest doses of heparin/Pitkin menstruum. The response to the treatment program was noteworthy, so much so that he has now resumed the practice of ophthalmology.

CASE 12.—S. L., a 47-year-old white man, a designer by occupation, was admitted to the Jewish Hospital of Brooklyn on June 12, 1947. This patient with atherosclerotic cardiovascular disease and parkinsonism had an acute attack of coronary artery thrombosis about one year prior to his present admission for which he was treated with the customary six weeks of bed rest. Ten days before admission he sustained trauma to the left tibia. Several days later he had pain in the left popliteal fossa which lasted twenty-four hours. Six days prior to admission he developed pain in the left chest which was sudden in onset and associated with dyspnea and shock. A diagnosis of coronary thrombosis with myocardial infarction was made and the patient put at bed rest. Two days later he developed a second episode of left axillary chest pain with severe dyspnea and was told that he had developed pneumonia which, however, did not respond to penicillin therapy. On the day of admission, the patient was in partial collapse, dyspneic, and cyanotic. The heart sounds were distant and there was a diastolic gallop rhythm with an impure first sound; congestive râles were audible over the posterior aspect of the lungs. The blood pressure was 106/60, as contrasted with his usual pressure of 170/90. The diagnosis was thromboembolic disease complicating acute coronary thrombosis with myocardial infarction. The presence of a posterior wall lesion was borne out by electrocardiograms taken on, and subsequent to, admission. The prognosis was considered to be extremely grave and, because of the advanced condition, prompt recourse was had to anticoagulation therapy as the only possible remedial measure. Heparin/Pitkin menstruum therapy was inaugurated immediately and continued for a period of twenty-five

this reason, we employed three injections of 0.2 Gm. of bismuth subsalicylate in oil, five days apart, before starting penicillin. For a variety of reasons, however, not all patients received this preliminary treatment.

MATERIAL STUDIED

The material in this report consists of the study of thirty-nine patients with cardiovascular syphilis. Thirty had aortic insufficiency and nine had saccular aneurysm or aneurysmal dilatation of the aorta.

An additional twenty-two patients in whom syphilis of the cardiovascular system was suspected have been treated with penicillin. Eighteen of these patients, all of whom had been admitted for treatment of neurosyphilis, were diagnosed as having uncomplicated aortitis. Four had aortic insufficiency and serologic findings indicative of syphilis, but rheumatic fever could not be excluded as the etiological factor in the cardiac involvement. These twenty-two patients are not included in this study, but it may be stated that no untoward reactions were observed in this group after the institution of penicillin therapy.

OBSERVATIONS

Aortic Insufficiency.—The age, sex, and color distribution of the thirty patients with syphilitic aortic insufficiency are summarized in Table I.

In addition to aortic insufficiency, eight patients also had aneurysmal dilatation of the aorta, one had saccular aneurysms of the arch of the aorta and of the innominate artery, and four were suspected of having coronary ostial stenosis. Twenty of the thirty patients gave a history of diminished cardiac reserve for periods of one month to five years prior to admission, and nine had had at least one bout of congestive heart failure.

Eight of the thirty patients had had no previous antisyphilitic treatment; only three of the remaining twenty-two had had as many as twenty injections of bismuth and twenty of arsenical drugs.

Treatment: Three of the eight patients who had had no previous antisyphilitic therapy received no preliminary treatment with bismuth. Four of the remainder received three injections of 0.2 Gm. of bismuth subsalicylate in oil, and one received only two bismuth injections before penicillin was started.

The twenty-two patients who had had some previous antisyphilitic treatment were not given preliminary bismuth, although some had received no antisyphilitic therapy for several years.

Penicillin was given in full dosage from the start of treatment (30,000 to 50,000 units every three hours). Total dosage was 3 to 6 million units. Three patients received penicillin in oil and beeswax (300,000 to 600,000 units daily), totaling 4.2, 7.2, and 9.0 million units, respectively.

Results: There were no untoward reactions attributable to penicillin therapy in any of these patients. Three presented cardiac symptoms during treatment. One of the three had been admitted in congestive heart failure with a history of precordial pain and paroxysmal dyspnea, and he had had two bouts

of heart failure in the year prior to admission. After treatment for congestive heart failure, penicillin was started without preliminary bismuth. During the first week of treatment the patient experienced several bouts of precordial pain no different from his previous attacks; during the second week of penicillin he experienced no untoward symptoms. He died in his fourth bout of congestive heart failure two months after the completion of penicillin treatment. The second of these patients was admitted in congestive heart failure with a history of precordial pain and paroxysmal dyspnea for an undetermined period before admission. She did not respond to the usual measures for congestive heart failure, and penicillin was started after she had received three injections of bismuth. She remained in congestive heart failure and died five weeks after penicillin therapy. Neither of these patients had had previous antisyphilitic therapy. It was considered that the natural course of the disease prevailed in these two patients.

A third patient gave a history of diminished cardiac reserve for two years prior to admission. He had had "several" bouts of congestive heart failure during this time, with precordial pain and nocturnal paroxysmal dyspnea, and had been on digitalis for one year. He experienced symptoms during penicillin therapy similar to his previous attacks. When seen two months after treatment, he stated that he had not had nocturnal paroxysmal dyspnea, and he was fairly well compensated.

There were no untoward symptoms during or after penicillin therapy in the remaining twenty-seven patients.

Aneurysm.—Four patients with saccular aneurysm and five with diffuse aneurysmal dilatation of the aorta were treated with penicillin (Table II).

TABLE II. SACCULAR ANEURYSM AND ANEURYSMAL DILATATION

PATIENT	SEX	COLOR	AGE ON AD-MIS-SION	AGE AT C-V DIAG-NOSIS	C-V DIAG-NOSIS	C.N.S. DIAG-NOSIS	KNOWN DURATION OF SYPHILIS (YEARS)	PREVIOUS ANTI-SYPHILITIC TREATMENT	C-V SYMP-TOMS	PENICILLIN	DATE	PRELIMINARY BIS-MUTH
Br	M	W	55	55	A.D.	T.D.	36	Adequate	0	3.4	6/46	0
Ea	M	B	47	47	A.D.	T.D.	Admission	0	0	6.0	3/46	0
Fr	M	W	51	50	S.A.	T.D.	31	Inadequate	+	6.0	2/47	2
Ga	M	W	71	71	Mul-tiple S.A.	M.V.	Admission	0	0	9.0POB	12/47	0
Jo	M	B	43	43	A.D.	T.P.	31	Adequate	0	6.0	9/45	0
Na	M	W	50	50	A.D.	A.N.S.	20	Adequate	0	2.0	4/45	0
No	M	W	63	61	S.A.	0	Unknown	Inadequate	0	4.0	5/47	0
Po	M	Y	53	53	A.D.	T.D.	Unknown	Inadequate	0	6.0	9/45	0
									0	6.0	7/46	0
Sz	F	W	46	46	S.A.	M.V.	18	0	0	6.0	3/47	0

C-V, cardiovascular.

A.D., aneurysmal dilatation of aorta.

S.A., saccular aneurysm of aorta.

†C.N.S., central nervous system.

T.D., tabes dorsalis.

M.V., meningovascular syphilis.

A.N.S., asymptomatic neurosyphilis.

T.P., taboparesis.

P.O.B., penicillin in oil and beeswax.

Only one patient had symptoms referable to the aneurysm. In this patient, pressure on the left main bronchus had produced secondary pulmonary changes, and he has since died.

Three patients had had large amounts of previous antisyphilitic treatment with heavy metals and arsenical drugs. Three had had no previous treatment; they did not receive preliminary treatment with bismuth. No reaction of any kind was noted in the penicillin treatment of these patients. With the exception of the one patient who died, all were asymptomatic when last seen.

DISCUSSION

In the syphilis clinic at Bellevue Hospital we have long believed that the gloomy prognosis of syphilitic aortic insufficiency, frequently found in the literature, was not justifiable. The report of Reader and coauthors⁸ offers evidence that the prognosis of this disease is better than was previously believed, and that this holds true not only for patients without diminished cardiac reserve but also for the symptomatic group. Our own experience has been similar to that reported from New York Hospital. For this reason, we believe that every patient with cardiovascular syphilis should be treated, if he has not previously had adequate antisyphilitic therapy.

We believe that until much larger series of patients have been observed, it is wise to use preliminary bismuth medication before starting penicillin. The use of small doses of penicillin to avoid Herxheimer reactions, as originally suggested by Moore,² is no longer advised. Moore has pointed out that it is now difficult to define a "small dose" of penicillin, in view of the report of Tucker and Farmer⁴ that febrile Herxheimer reactions occurred during the treatment of late syphilis after doses of penicillin as small as 500 units.

Differential Diagnosis.—The difficulty occasionally encountered in making a differential diagnosis between syphilis and rheumatic fever as the etiological agent of aortic insufficiency is brought out well by one patient previously mentioned.

This 48-year-old white woman had had five bouts of congestive heart failure in the three years prior to admission to this service. She had been carried on one of the medical services as a rheumatic cardiac with mitral insufficiency and stenosis, and aortic insufficiency. A positive serologic test for syphilis was discovered two and one-half years earlier, and she had received eighteen injections of an arsenical and eighteen of bismuth up to one year before admission to this service. Because of positive spinal fluid findings for syphilis she was transferred to us for antisyphilitic therapy. She received 4 million units of penicillin in aqueous solution.

Following penicillin therapy, marked diminution of cardiac reserve continued, and subsequently the patient was twice admitted to the medical service in congestive heart failure. Fourteen months after treatment she was admitted in coma with a right hemiplegia. The cardiac rhythm was auricular fibrillation. It was believed that her course had been typical of rheumatic heart disease with the terminal episode due to cerebral embolization from left-sided mural thrombi.

Necropsy revealed that she had syphilitic aortitis with stenosis of the coronary ostia and syphilis of the aortic valve with insufficiency. The mitral valve was normal. There were thrombi in both auricular appendages and infarcts in the brain, lungs, spleen, and kidneys.

Clinical Improvement Following Penicillin Therapy.—As seen in Table I, seven of the patients with aortic insufficiency "claim to be improved" after treatment. Table I shows that of these seven patients, one denied symptoms of diminished cardiac reserve on admission but later said he had had dyspnea on exertion; three described dyspnea on exertion (one with precordial pain); one described dyspnea on exertion and nocturnal paroxysmal dyspnea; and two had been in congestive heart failure, with histories of precordial pain and nocturnal paroxysmal dyspnea. The last two patients were on digitalis at the time of treatment and have continued it since. All seven patients are working at present, and claim to be able to do more work with less discomfort than formerly. Adequate antisyphilitic therapy is expected to arrest a syphilitic inflammatory process in the aorta, but it is difficult to attribute an increase in cardiac reserve to the arrest of such a process. We believe that the apparent improvement in cardiac reserve noted by these patients is due to a general systemic improvement following the eradication of the chronic low-grade syphilitic infection.

CONCLUSIONS

1. Thirty-nine patients with cardiovascular syphilis (thirty with aortic insufficiency and nine with saccular aneurysm or aneurysmal dilatation of the aorta) were treated with penicillin in full dosage from the start of treatment.
2. No untoward reactions attributable to penicillin were observed.
3. It is believed that the danger of Herxheimer reactions has been over-emphasized, but until much larger series of patients have been observed, it is advisable to administer bismuth before starting penicillin in patients who have received no previous antisyphilitic therapy.

ADDENDUM

To May, 1949, fifty patients with aortic insufficiency and ten patients with aneurysm were treated with penicillin. There were no adverse reactions encountered in this group.

REFERENCES

1. Dolkart, R. E., and Schwemlein, G. X.: The Treatment of Cardiovascular Syphilis With Penicillin, *J. A. M. A.* **129**:515, 1945.
2. Moore, J. E.: *Penicillin in Syphilis*, Springfield, Ill., 1946, Charles C Thomas, Publisher.
3. Callaway, J. L., Noojin, R. O., Flower, A. H., Jr., Kuhn, B. H., and Riley, K. A.: Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, *Am. J. Syph., Gonorr., & Ven. Dis.* **30**:110, 1946.
4. Tucker, H. A., and Farmer, T. W.: Penicillin in Cardiovascular Syphilis, *Arch. Int. Med.* **80**:322, 1947.
5. Russek, H. I., Cutler, J. C., Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis With Penicillin, *Ann. Int. Med.* **25**:957, 1946.
6. Hill, W. R.: Problems Arising in the Treatment of Syphilis With Penicillin, *New England J. Med.* **235**:919, 1946.
7. Woodruff, I. O.: Cardiovascular Syphilis, *Am. J. Med.* **4**:248, 1948.
8. Reader, G. G., Romeo, B. J., Webster, B., and McDermott, W.: The Prognosis of Syphilitic Aortic Insufficiency, *Ann. Int. Med.* **27**:584, 1947.

MITRAL STENOSIS: AN EXPERIMENTAL STUDY OF PULMONARY-AZYGOS VENOUS ANASTOMOSIS

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IN RECENT years attention has been directed toward surgical procedures designed to improve or restore to normal the pathologic physiology resulting from congenital or acquired defects in the cardiovascular system. Several very valuable operations have been evolved, most of which, such as the ligation of patent ductus arteriosus as devised by Gross¹ and the arterial shunt in pulmonary stenosis as devised by Blalock and Taussig² and modified by Potts and co-workers,³ are aimed primarily at alterations of blood flow on the arterial side of the vascular tree. The long history of the operative repair of arteriovenous aneurysms has been that of a steady increase in understanding and improvements in the operative repair of a physiologic abnormality in blood flow. At least one procedure on the arterial side, however, is aimed to alter not primarily blood flow, but to relieve intravascular pressure. This consists of the repair of coarctation of the aorta as devised independently by Craaford⁴ and by Gross.⁵ The primary merit of this procedure is that the operation removes the cause of the abnormal physiology and restores the circulatory system to the normal status, and thus aborts the ill effects on other organs which develop secondarily. On the venous side of the systemic circulation, the portocaval and lienorenal shunt procedure, as advocated by Blakemore and Lord,⁶ is likewise devised to reduce abnormal intravascular pressure. This procedure is still in the early stages of evaluation, and is unlike the repair of coarctation in that the primary cause of hypertension is not removed. The operation is akin to an escape valve to allow release of pressure by virtue of flow through the new channel.

A very similar type of operation on the venous side of the pulmonary circuit has been devised for potential use in conditions in which there is hypertension in the pulmonary veins. Of these conditions, mitral stenosis is by far the outstanding clinical example. It is the purpose of this paper to outline the experimental observations which have been made relative to the making of such a pulmonocaval venous shunt.

The exact pathogenesis of right-sided heart failure following stenosis of the mitral valve has never been established by adequate experimental or clinical data. Most of the evidence is indirect, but it is of such a compelling nature that there exists a general consensus as to the mechanism of this phenomenon.

From the Halsted Surgical Experimental Laboratory, University of Colorado Medical Center.
Supported by United States Public Health Service Research Grant R-86.

Presented at the Meeting of the Rocky Mountain Section of the Society for Experimental Biology and Medicine, May 22, 1948, Denver, Colo.

It is thought that by virtue of the narrowing of the valve, blood flow through it is impeded. Blood dammed back into the left auricle and venous pulmonary system increases the pressure within that system. With the increase in pressure, flow through the valve is augmented, but gradual dilatation of the left auricle occurs, and the pressure within the system over a period of time continues to mount. This pressure is transmitted throughout the capillary system on to the arterial side of the pulmonary tree. With this increased resistance, pulmonary arterial pressure rises, and the work of the right heart is correspondingly increased. Changes in the pulmonary arterioles and capillaries accompany this increase in pressure. Although the output of the right heart is not materially increased, its work load is augmented because of this phenomenon of pressure. The right side hypertrophies under these conditions and gradually comes to failure.

This theory is substantiated by many clinical observations: the dilatation of the left auricle, the prominence of the pulmonary vascular tree, the frequent occurrence of pulmonary hemorrhage, the loud snapping sound of the pulmonary valve, and, finally, the enlargement of the right ventricle and eventual failure. It is to be observed that the underlying physiologic abnormality on which this chain of events is predicated is an increase of pressure in the pulmonary venous tree. This concept, however, has not been substantiated by actual direct measurements either in man or in animals. The technical difficulty of creating experimental mitral stenosis has proved a severe stumbling block in the study of this condition. Until the advent of the cardiac catheter, measurement of the pulmonary artery pressure in man was unobtainable. Since that time a paucity of measurements of the pulmonary artery pressure in patients with mitral stenosis have been published in the literature. Direct measurement of the pulmonary venous pressures in man is still unobtainable. However, in spite of this lack of direct confirmatory data, because of the strong circumstantial evidence, the pressure mechanism of the pathogenesis of right ventricular failure in mitral stenosis has become widely accepted.

If this mechanism exists, it might be desirable to attempt to reduce the venous pressure in the pulmonary circuit in an effort to forestall or prevent the subsequent chain of events leading to cardiac failure. It is technically feasible to create a venous shunt between the pulmonary vein and the superior vena cava. The technique for accomplishing this in experimental animals is herein described.

However, it is not at all certain that this procedure would necessarily be of value in patients with obstruction of the mitral valve. The extent to which blood flow through the stenosed valve is dependent on the venous pressure (left atrium and pulmonary veins) is not known. It is entirely conceivable that reduction of this pressure may significantly diminish flow through the valve and thus seriously jeopardize the output of the left ventricle. It is also clear that whatever blood flows from this shunt must immediately enter the right auricle and again be sent through the right ventricle to the lungs. There will thus be a "circus movement" of blood which repeatedly traverses the right

ventricle, and the output of this side of the heart must increase to maintain the output of the left ventricle (Fig. 1). Whether in the long run this increase in output, which presumably would occur at a normal pressure level as far as the right ventricle is concerned, would be less injurious to the right ventricle than a smaller output at a higher pressure level is not as yet known. Accordingly, the theoretical merit of this procedure is open to serious question and must be the subject of further evaluation.

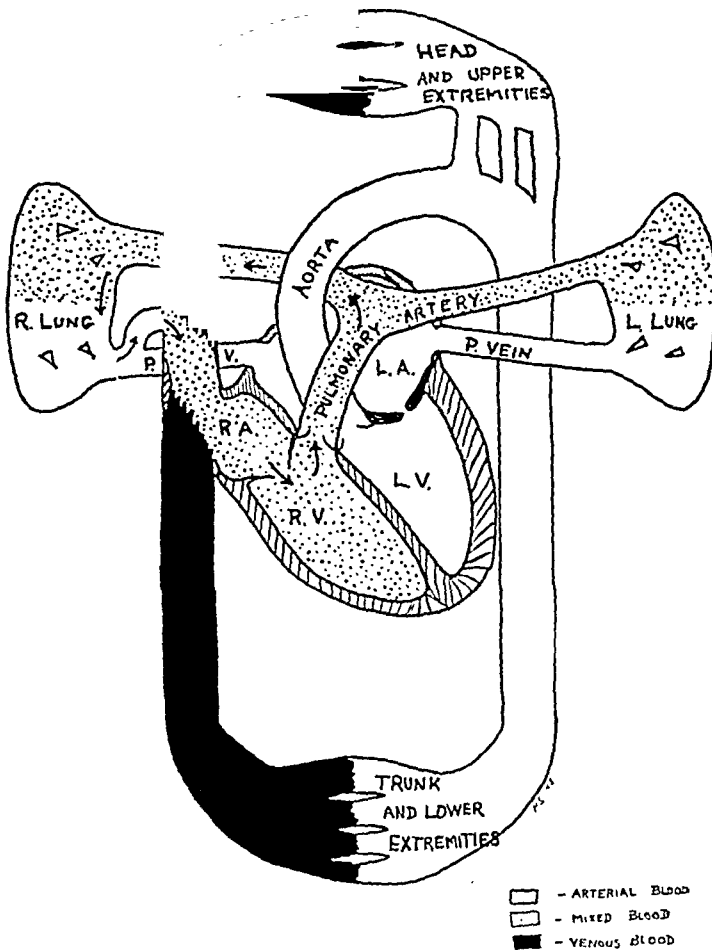


Fig. 1.—Diagram of circulation in mitral stenosis after creation of pulmonary-azygos venous shunt. Arrows show path taken by blood recirculating through right ventricle.

EXPERIMENTAL PROCEDURES

At first approach to this problem it seemed that there were three possibilities of effecting a left-to-right venous shunt. The first would most obviously be an interauricular septal defect. Second, an orifice could be made between the right pulmonary vein and the right auricle. And third, an anastomosis could be made between a pulmonary vein and a systemic vein. An interauricu-

lar septal defect can be made without too much difficulty in the experimental animal. This procedure, however, is subject to some risk, and the size of the orifice cannot always be thoroughly controlled. Moreover, intra-auricular thrombosis occasionally occurs. In the second instance, a side-to-side anastomosis of the pulmonary vein to the right auricle was subject to the same criticism, although an end-to-side return of the pulmonary vein to the right auricle is technically quite feasible. The most likely possibility appeared to be, therefore, the use of a systemic vein with anastomosis to the pulmonary vein, and the most obvious vein available for this purpose was the azygos vein, because of its relatively large size and its proximity to the right pulmonary vein as it arches over to the root of the right lung. This method was therefore adopted for study.

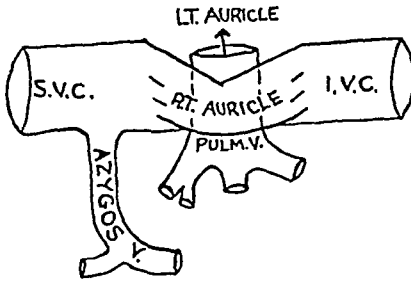
The first attempt was to make a suture anastomosis between the proximal end of the divided azygos vein and the side of the exposed right pulmonary vein (Fig. 2,B). This maneuver was found to be fraught with considerable technical difficulties because of the friable nature of the wall of the pulmonary vein in dogs. Even when this procedure was successfully performed, however, in the normal animal there was uniform occlusion of the opening from thrombosis at the site of anastomosis. This was not surprising, and demonstrated the well-known difficulty encountered in venous anastomosis when there is no pressure gradient between the two ends of the shunt. Frequent measurements of the pressures within the pulmonary vein and the vena cava in the normal dog (open chest) revealed that there is seldom more than 3.0, and never more than 5.0 cm. of water difference between the two systems.

A similar fate was met with the Vitallium tube technique when an end-to-side anastomosis was made (Fig. 2,C). Here the difficulty was slightly different in nature. If a tube of adequate size (5.0 to 8.0 mm. in diameter) was inserted into the side of the pulmonary vein, enough puckering occurred with the insertion of the encircling ligatures to force the tube well into its lumen and into the orifice where the right pulmonary vein enters the left auricle. This materially obstructed the flow of blood through the vein and thrombosis within the tube likewise still occurred. Because of the mechanical obstruction by this method, it was felt that except in the presence of a considerably dilated pulmonary vein, this threat to pulmonary venous flow was such as to make an end-to-side tube anastomosis a procedure of doubtful merit.

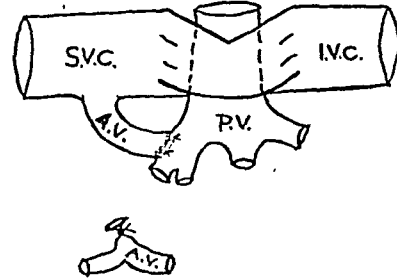
Accordingly, effort was directed toward constructing an end-to-end anastomosis between the proximal end of the ligated azygos vein and the proximal end of the divided branch of the pulmonary vein which led from the right upper lobe of the lung (Fig. 2,D and E). In most animals these structures are of approximately the same size. It was not perfectly clear, from the available literature, what would be the fate of the upper lobe of the lung when its vein was ligated and divided. This problem, therefore, was studied experimentally and the result has been previously published.⁷ Although there is an immediate intense engorgement of the pulmonary parenchyma and the alveolar spaces, there occurred no necrosis of the pulmonary tissue, and after a period of about four months,

with the resorption of the hemorrhagic exudate and formation of venous collateral, the pulmonary tissue returned almost, although not quite to normal.

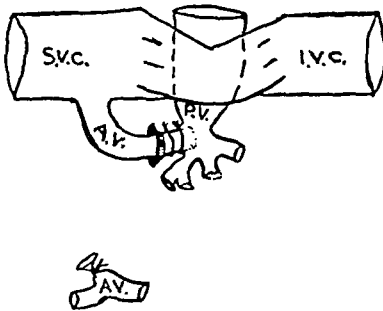
Since there was very little pressure gradient existing in the animal between the pressures in the superior pulmonary vein and vena cava, the value of



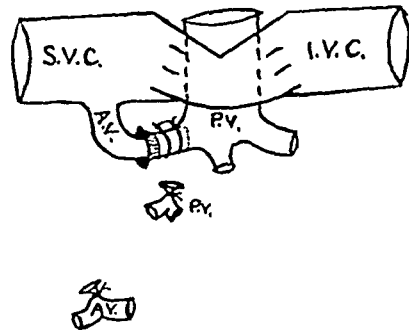
A. NORMAL ANATOMICAL RELATIONS



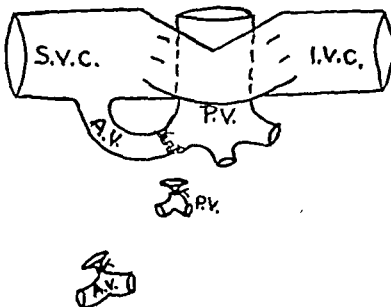
B. END-TO-SIDE, AZYGOS-PULMONARY SUTURE ANASTOMOSIS



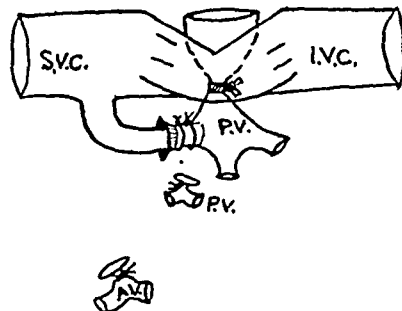
C. END-TO-SIDE, AZYGOS-PULMONARY TUBE ANASTOMOSIS



D. END-TO-END, AZYGOS-UPPER BRANCH PULMONARY. TUBE ANASTOMOSIS



E. END-TO-END, AZYGOS-UPPER BRANCH PULMONARY. SUTURE.



F. END-TO-END AS IN "D" LIGATION PULMONARY VEIN

Fig. 2.—Diagrammatic illustrations of various experimental procedures. Plan "D" is the method of choice in experimental animals.

dicoumarin in preventing venous thrombosis within the anastomosis was examined. In the dog, dicoumarin is a treacherous drug, since the response is quite variable from animal to animal, and the margin of safety in terms of dosage in any one animal is small. It was difficult to obtain a steady elevation in prothrombin time, or to correlate the prothrombin time to the bleeding tendency. In many animals in which there was an elevation of only three to four seconds over the normal (nineteen seconds in normal animals, using whole blood with Difco's thromboplastin), a marked bleeding tendency was apparent. In every animal on which operation was performed and in which the prothrombin time had been increased, death occurred from hemorrhage, although in one animal the operation had proceeded no further than rib resection.

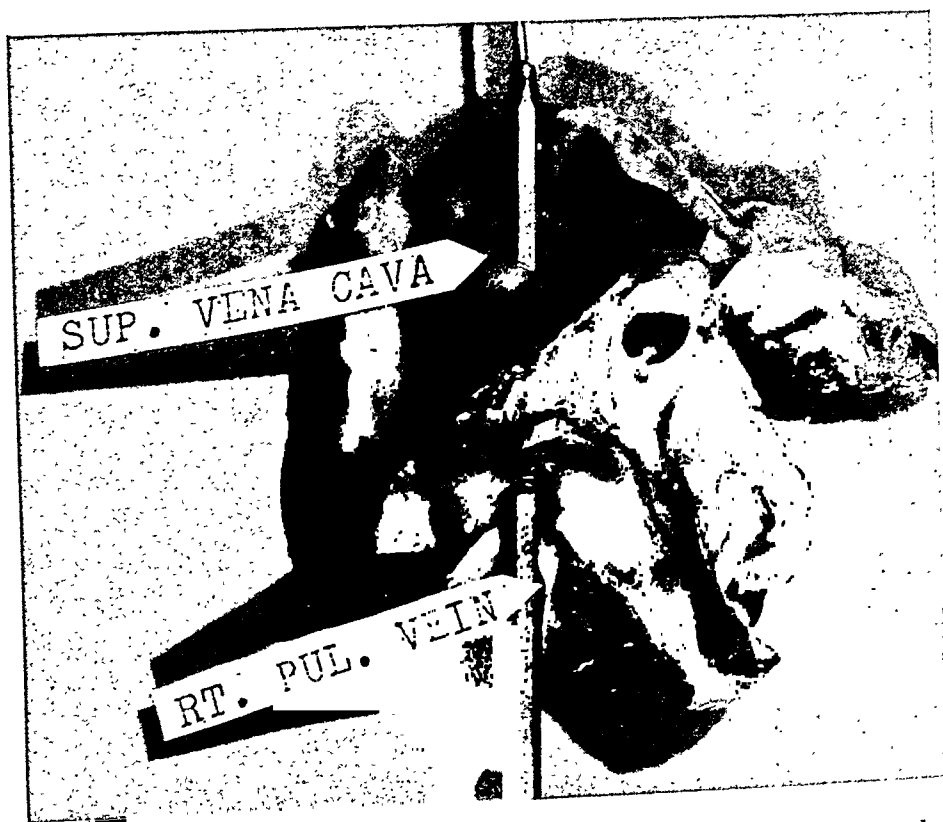


Fig. 3.—Photograph of specimen from Dog 48-24. Probe handle passes easily through the shunt.

A technique of giving the animal dicoumarin approximately eighteen hours before operation was therefore devised. At the time of operation, the prothrombin time was normal. Between six and twenty-four hours following operation the prothrombin times were elevated, but as has been mentioned, a persistent elevation without marked variation was not obtained. However, when use was made of an end-to-end Vitallium tube anastomosis between the proximal ends of the azygos vein and the upper lobe branch of the right pulmonary vein, accompanied by this method of dicoumarin administration, a patent anastomosis was consistently obtained (Fig. 3).

It was observed, however, that the caliber of that part of the vein which traversed the Vitallium tube was narrowed by perivascular fibrosis which oc-

curred between the tube and the vein. Thus, when a 5.0 mm. tube was used, the effective diameter of the shunt would be reduced to about 3.0 millimeters.

In order to evaluate the importance of a differential in pressure, a series of animals was done in which an end-to-end type of anastomosis was made, following which the pulmonary vein proximal to the anastomosis was either partially or completely occluded by ligature (Fig. 2,*F*). It was felt that this obstruction to the return flow of the blood in the vein to the left auricle would increase the pressure in this vein and would partially simulate the venous hypertension of mitral stenosis. This was found to be the case, and anastomoses created in this fashion remained widely patent without thrombosis or narrowing. An end-to-side suture anastomosis, however, in the presence of total pulmonary venous ligation, gradually thrombosed and was obliterated.

Table I gives a summary of the results in these experiments.

All operations were performed under strictly aseptic conditions, using intravenous barbiturate anesthesia with a mechanical respirator. Mongrel dogs of various sizes were used, although attempt was made to use larger animals weighing 10 kilograms or more. Observations were made at intervals following the anastomosis varying from three weeks to as long as four months.

The operative procedure was briefly as follows:

Exposure was obtained through an anterolateral incision in the fourth right intercostal space. The azygos vein was first dissected free, and then ligated just at the point where the first major branch from the upper intercostal veins enter. In most animals this gave a length of about two inches. A bulldog clamp was applied near the vena cava, and the vessel was cut just proximal to the ligation. A small moist pack was placed over the vein to avoid desiccation. Attention was now directed to the pulmonary vein. A few cubic centimeters of 2 per cent Novocain were injected into the pericardium to minimize the possibility of serious cardiac arrhythmias. The pericardium was grasped just above the phrenic nerve with two Allis forceps and traction exerted upward. Incision was now made between the pulmonary vein and the pericardium and dissection was carried inward, separating the pulmonary vein from the right auricle. This part of the procedure was always delicate and time consuming. The pulmonary vein was finally freed posteriorly and was thus mobilized almost to its entrance into the left auricle. The operation was now completed by making the desired type of anastomosis, and then closing the chest wall, making sure the lungs were well inflated. The animals tolerated this procedure without difficulty.

COMMENTS

The use of dicoumarin in dogs gave rise to many technical difficulties and was found to be completely unnecessary when a pressure gradient was introduced. This would parallel the situation to be expected in the clinical patient with mitral stenosis. The end-to-end type of anastomosis, with the subsequent engorgement of the upper lobe of the lung, would appear to be less desirable than an end-to-side anastomosis, at least in theory. In the presence of a dilated pulmonary vein, the end-to-side anastomosis using the tube technique

TABLE I. SUMMARY OF EXPERIMENTAL RESULTS

DOG	PROCEDURE	DATE OPERATION	DATE AUTOPSY	CALIBER OF LUMEN (MM.)	SUMMARY
No Dicoumarin or Pressure Gradient					
46-40	End-to-side, suture, satisfactory	5-20-46	6- 4-46	0	No patent anastomosis obtained in the eight dogs surviving operation; in addition, two operative deaths from hemorrhage
46-48	End-to-side, suture, constricted	5-23-46	6-26-46	0	
46-50	End-to-end, suture, satisfactory	5-30-46	6-26-46	0	
46-58	End-to-end, tube 4 mm., satisfactory	6-21-46	8-13-46	0	
46-61	End-to-side, tube 5 mm., poor	7-15-46	8-13-46	0	
46-75	End-to-end, tube 5 mm., satisfactory	11-13-46	12-10-46	0	
47-35	End-to-end, tube 4 mm., satisfactory	8-12-47	9-10-47	0	
47-36	End-to-end, tube 6 mm., satisfactory	8-13-47	9-10-47	0	
Dicoumarin; No Pressure Gradient					
47-3	End-to-end, tube 4 mm., satisfactory	1-31-47	2-26-47	2	A patent anastomosis was obtained in seven of nine dogs surviving three days or more; all anastomoses narrowed by perivascular fibrosis; in addition, three postoperative deaths from hemorrhage (dicoumarin)
47-4	End-to-end, tube 5 mm., satisfactory	2- 3-47	2- 5-47	5	
47-6	End-to-end, tube 5 mm., satisfactory	2-14-47	3- 4-47	1	
47-10	End-to-end, tube 4 mm., inadequate dicoumarin	3- 3-47	3-20-47	0	
47-12	End-to-end, tube 5 mm., satisfactory	3- 7-47	3-26-47	2	
47-16	End-to-end, tube 7 mm., satisfactory	3-21-47	3-26-47	6	
47-34	End-to-end, tube 6 mm., satisfactory	7-10-47	7-28-47	2	
47-36	End-to-end, tube 6 mm., satisfactory	7-15-47	8- 4-47	2	
47-40	End-to-side, tube 6 mm., poor	7-22-47	8-20-47	0	
No Dicoumarin; Pressure Gradient (Partial Ligation of Pulmonary Vein)					
47-102	End-to-end, tube 5 mm., satisfactory	1- 9-48	1-29-48	5	All five end-to-end tube anastomoses widely patent; two end-to-side suture anastomoses became occluded; no operative or post-operative mortality
48-19	End-to-end, tube 6 mm., satisfactory	1-14-48	3-15-48	4	
48-23	End-to-end, tube 7 mm., satisfactory	1-26-48	3-15-48	3	
48-22	End-to-end, tube 5 mm., satisfactory	2- 2-48	3-15-48	4	
48-24	End-to-end, tube 6 mm., satisfactory	2-16-48	3-15-48	4	
48-28	End-to-side, suture, satisfactory	3-23-48	4-19-48	0	
47-77	End-to-side, suture, satisfactory	3-24-48	4-19-48	0	
No Dicoumarin; Pressure Gradient (Complete Ligation Pulmonary Vein)					
48-18	End-to-end, tube 7 mm., satisfactory	1-16-48	2-16-48	6	Both procedures resulted in widely patent anastomoses; one post-operative death
47-86	End-to-end, suture, satisfactory	3-23-48	4-19-48	4	

might be quite possible. However, the potential element of partial obstruction of the flow from this vein into the left auricle must not be overlooked. In the normal animal, ligation of the branch of the pulmonary vein to the right upper lobe is well tolerated; whether this would be equally true in a patient with mitral stenosis is open to question.

SUMMARY

1. The possibility of the creation of a venous shunt between the pulmonary vein and the superior vena cava by the use of a proximal segment of the azygos vein in patients with mitral stenosis and pulmonary venous hypertension is suggested. The effect upon cardiovascular hemodynamics of such a procedure remains to be investigated.

2. That such a shunt is technically feasible in dogs by means of an end-to-end anastomosis of the azygos and pulmonary veins, using a Vitallium tube, has been demonstrated.

3. In the presence of a pressure gradient such a shunt is well tolerated in normal animals and remains widely patent.

REFERENCES

1. Gross, R. E.: Surgical Ligation of a Patent Ductus Arteriosus; Report of First Successful Case, *J. A. M. A.* **112**:729, 1939.
2. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There is Pulmonic Stenosis or Pulmonary Atresia, *J. A. M. A.* **128**:189, 1945.
3. Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of the Aorta to a Pulmonary Artery, *J. A. M. A.* **132**:627, 1946.
4. Craaford, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, *J. Thoracic Surg.* **14**:347, 1945.
5. Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta, *New England J. Med.* **233**:287, 1945.
6. Blakemore, A. H., and Lord, J. W., Jr.: The Technique of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, *Ann. Surg.* **122**:476, 1945.
7. Swan, H., and Mulligan, R. M.: An Experimental Study of the Effect of Ligation of Pulmonary Veins in the Dog, *J. Thoracic Surg.* **17**:44, 1948.

THE PRECORDIAL ELECTROCARDIOGRAM IN INCOMPLETE RIGHT BUNDLE BRANCH BLOCK

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INTRODUCTION

IN 1917 Rothberger and Winterberg¹ published an electrocardiographic record which depicts the gradual clearing of a defect in conduction affecting the right branch of the bundle of His. An attempt to cut this structure in the course of an experiment on a dog blocked it only temporarily. Fortunately, one of the tracings taken spanned the period during which the injured bundle gradually recovered its conductivity. The investigators recognized that the central complexes of this record represent *incomplete right bundle branch block*. They are transitional in form between the preceding complexes, which are characteristic of complete block, and the subsequent complexes, which are of normal outline.

Some years later, Wilson and Herrmann,² without being aware of this earlier work, carried out an extensive experimental investigation in which the canine dextrocardiogram and levocardium were superimposed in varying time relations by a number of different methods. By producing right bundle branch block and then stimulating the anterior wall of the right ventricle just after the normal excitation wave had reached the left, they were able to produce at will complexes representing a delay in right ventricular activation of any magnitude less than that which occurs in complete right bundle branch block. Such complexes are identical with those of complete right bundle branch block with regard to the parts of the QRS wave written before excitation of the right ventricle begins; that is to say, before the excitation wave spreads to muscle normally excited via the right Purkinje plexus. They are transitional between bundle branch block complexes and normal complexes with regard to the length of the QRS interval and the form of the T wave.

The present report deals with the description, classification, and interpretation of clinical electrocardiograms which are intermediate, with regard to the form of the ventricular complex, between normal tracings and those which represent complete right bundle branch block, and which display a QRS interval measuring less than 0.12 second in the limb leads. We have attempted to establish criteria for the diagnosis of incomplete right bundle branch block and to

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The material upon which this article was based was collected with the aid of grants to F. N. Wilson from the Horace H. Rackham School of Graduate Studies and the S. S. Kresge Foundation.
*Work done as Clinical Fellow of the American College of Physicians for the year 1946.

learn something about its incidence and its clinical significance. Incomplete left bundle branch block has not been included in our study because of the difficulty of distinguishing the electrocardiographic changes which it produces from those that accompany enlargement of the left ventricle.

MATERIAL AND METHODS

The tracings studied were selected from a group of 39,778 electrocardiograms taken over a period of fifteen years. Among these we found 1,123 instances in which a definite or tentative diagnosis of a defect in intraventricular conduction of one kind or another had been made. We then examined those patients in whom both standard limb leads and multiple precordial leads had been taken. Since precordial leads are not taken routinely in this laboratory, we also investigated the accuracy of the impressions based on the standard and unipolar limb leads, which are taken in every case. There were 150 instances in which the extremity leads suggested that incomplete right bundle branch block might be present. In thirty-seven of these the precordial leads showed no evidence of a defect in intraventricular conduction. In the remaining 113 cases, the form of the QRS complexes of the leads from the right side of the precordium supported in a greater or lesser measure the view that activation of the right ventricle was abnormally delayed.

The limb leads considered suggestive of incomplete right bundle branch block displayed a QRS interval measuring 0.08 second or more, but less than 0.12 second, and a conspicuous broad S wave in Lead I. In some instances of this kind, the mean electrical axis was deviated to the left so that the electrocardiographic pattern bore a superficial resemblance to that produced by left ventricular enlargement and by incomplete left bundle branch block. In all such instances there were invariably small Q and S waves, as well as a dominant R deflection in Lead I. The presence of both a primary and a secondary R wave in the unipolar right arm lead (Lead V_R) was thought at first to be of value in detecting cases of incomplete right bundle branch block, but further investigation did not strongly support this impression.

One hundred seventy-two cases of complete right bundle branch block diagnosed on the basis of the changes in the precordial leads, were also reviewed in order to ascertain whether the variations in electrocardiographic pattern observed in incomplete right bundle branch block are or are not similar to those that occur when the block is complete.

CLASSIFICATION

Cases of incomplete right bundle branch block associated with myocardial infarction and with pulmonary embolism will be considered separately. The basis for the classification of the rest of our material has been the configuration of the QRS group in the leads from the right side of the precordium. The groups, subgroups, and classes distinguished are listed below. A primary R and a late R' deflection were present in one or more of Leads V_1 , V_2 , and V_E in all cases

except those in which a diagnosis of anterior infarction had been made, and one additional case which has been placed alone in Group VII.

Group I.—The R and R' waves of Lead V₁ are both small and of nearly the same size. The R' deflection does not exceed 5.0 mm. in height. If an S wave is present it is not over 5.0 mm. in depth (Fig. 7,A). This group contains twenty-eight cases.

Group II.—The primary and secondary R waves of Lead V₁ are separated by a deep S deflection always more and usually much more than 5.0 mm. in depth. This group contains twenty-two cases, which have been placed in two subgroups as follows:

A. The R and R' waves are both small and of about the same voltage (Fig. 7,B). This subgroup contains seventeen cases.

B. The R wave is small, but R' is between 5.0 and 10 mm. in height (Fig. 7,C). This subgroup contains five cases.

Group III.—The initial R wave is small and R' is at least 6.0 and usually more than 10 mm. in height. This group contains thirty cases. On the basis of the behavior of the two R deflections as the precordial electrode was moved to the left, they were divided into the following four subgroups:

A. The R' wave is largest in Lead V₁ or Lead V₂, becomes smaller with each successive lead, and is usually absent or inconspicuous in Lead V₃ or Lead V₄. In the leads from the left side of the precordium the R deflection is relatively small (Fig. 7,E). This subgroup contains eleven cases.

B. The tracings of this subgroup are similar to those of the preceding with regard to the size of the R' wave, but there are small initial R deflections and very deep S waves in the leads from the central part of the precordium, that is, in one or more of Leads V₂ to V₅. There are large R' waves in the leads from the extreme right side of the precordium and large R waves in the leads from the extreme left side of the precordium, but small R and deep S waves in the other precordial leads (Fig. 7,F). This subgroup contains eight cases.

C. The R' deflection is conspicuous only in Lead V₁ or in Leads V₁ and V₂. The initial R wave grows rapidly with each succeeding lead and is very tall in the leads from the extreme left side of the precordium. The transitional zone, yielding complexes intermediate in form between those obtained from the extreme right side and those obtained from the extreme left side of the precordium, is unusually far to the right (Fig. 7,G). This subgroup contains six cases.

D. As the exploring electrode is shifted to the left, the size of the R' decreases less rapidly than in subgroups A, B, and C, and is tall in the first three, four, or even five precordial leads. Instead of being replaced by an S wave in the leads from the transitional zone, it appears to approach the R deflection and become fused with it (Fig. 7,H). This subgroup contains six cases.

Group IV. This group includes cases of incomplete right bundle branch block associated with right ventricular hypertrophy. These are discussed in a separate section.

Group V. This group contains eleven cases of myocardial infarction.

Group VI. This group contains two cases of pulmonary embolism.

Group VII. This group contains only one case. All the precordial leads yielded complexes which are transitional in form (Fig. 9).

Our cases were also classified on the basis of the number of precordial leads showing evidence of a conduction defect suggestive of incomplete right bundle branch block, as follows:

Class a.—In forty-seven cases changes of the kind in question were present in Leads V_1 , V_2 , and V_E .

Class b.—In thirty-six cases there was no late R' deflection in Lead V_E , but such a deflection was present in Leads V_1 and V_2 .

Class c.—In five cases R and R' waves were present in Leads V_1 and V_E , but there was no secondary R' wave in Lead V_2 .

Class d.—In twenty-four cases R and R' waves were conspicuous in Lead V_1 only.

Class e.—In thirteen cases an initial and a secondary R wave were present in Lead V_1 or in Leads V_1 and V_2 , but Lead V_E had not been taken. These cases were at first placed in this class. Later those cases in which R and R' waves were present in Lead V_1 only were added to Class d and those in which these deflections occurred in Lead V_2 as well were added to Class b .

TABLE I. CLASSIFICATION OF INCOMPLETE RIGHT BUNDLE BRANCH BLOCK

GROUP	a	b	c	d	TOTAL	CORRECTED TOTAL	PROBABLE CASES
I	14	9	1	4	28	27	1
II	9	7	3	3	22	20	2
III	3	4	0	12	19	11	8
IV, A	7	3	0	1	11	10	1
IV, B	2	5	0	1	8	7	1
IV, C	5	1	0	0	6	6	0
IV, D	2	3	0	0	5	5	0
V	4	4	0	3	11	8	3
VI	1	0	1	0	2	2	0
VII	—	—	—	—	1	1	0
Total					113	97	16

Table I shows the distribution with respect to classes of the cases placed in each of the groups or subgroups. The column headed "Total" gives the sum of the numbers which appear on the same horizontal line in the four preceding columns. The column headed "Corrected Total" gives the sum of the figures lying on the same horizontal line and in the columns headed "a," "b," and "c," plus a number representing cases placed in Class d , in which the evidence pointing to incomplete right bundle branch block exhibited by the standard precordial leads was supported by data furnished by unipolar leads from points to the right

of the right sternal margin, or by other records depicting complete right bundle branch block in the same patient. The column headed "Probable Cases" gives the difference between the figure in the sixth column and that in the seventh.

There were nineteen cases in which the records taken disclosed a variation in the grade of the defect in conduction. In four instances both complete and incomplete right bundle branch block were recorded. In the remainder, which are not included in our series of cases of incomplete right bundle branch block, partial or transient complete right bundle branch block was observed.

CASES SHOWING VARIATIONS IN THE GRADE OF THE CONDUCTION DEFECT

The least questionable cases of incomplete right bundle branch block are those in which complexes typical of complete right bundle branch block and complexes transitional in form between these and complexes of normal outline occur either in the same record or in the same set of records. For this reason, we have selected two cases of this kind for discussion. In order to bring out more

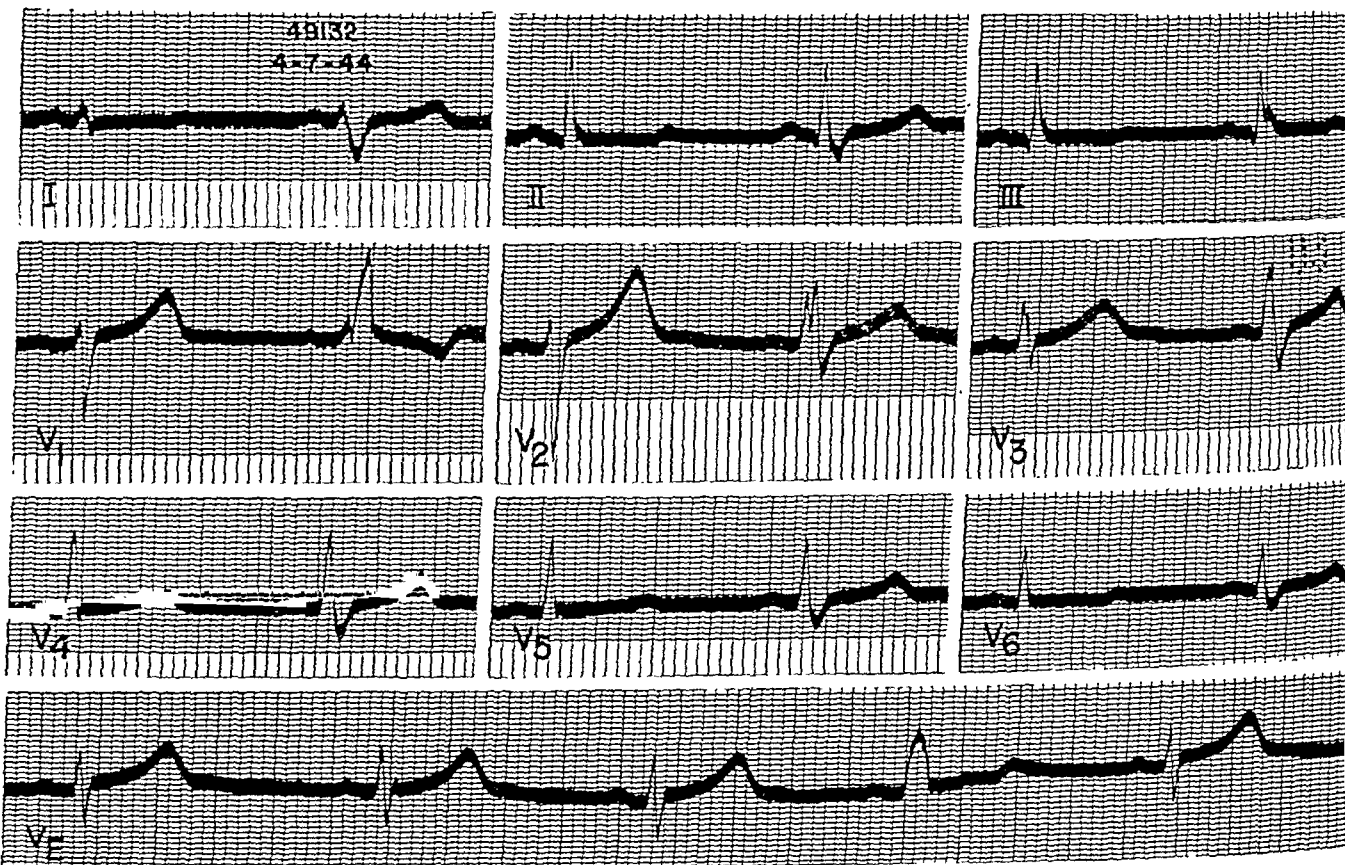


Fig. 1.—Partial right bundle branch block. The first complex of each pair represents normal intraventricular conduction; the second, complete right bundle branch block. (Reproduced with the permission of Interscience Publishers, Inc.)

clearly the similarities and differences between the two types of complexes, we have in some instances superimposed them photographically by the following procedure:

The film negative of the original electrocardiogram was printed as a positive on another strip of film. Both the negative and the positive were then put in a photographic enlarger, and a complex representing complete right bundle branch block was superimposed, in the proper time relation, upon one representing incomplete right bundle branch block, or, in one instance, normal intraventricular conduction. This was done by shifting the two complexes until the P waves and the earliest QRS components coincided, while keeping the two sets of time lines, the two sets of horizontal lines, and the two isoelectric levels parallel. The enlarged photograph made in this way shows a white and a black tracing, one upon the other, with white grid lines belonging to the first and black grid lines belonging to the second. Where black and white deflections or lines coincide the resulting tone is gray.

For purposes of comparison and orientation, we shall present first a case of partial right bundle branch block in which complexes typical of complete right bundle branch block and complexes of normal contour occurred in the same record.

The patient, a man 40 years of age, was found to have a defect in intraventricular conduction when an electrocardiogram was taken elsewhere, on Sept. 8, 1941, in the course of a routine examination. At a later date, May 24, 1943, another tracing showed normal intraventricular conduction; but on Dec. 17, 1943, right bundle branch block was again present. There were no complaints referable to the heart, and the physical examination was entirely negative. The electrocardiogram taken on April 7, 1944, at the University Hospital shows in all leads a succession of ventricular complexes typical of complete right bundle branch block, alternating with runs of complexes of normal outline. In Fig. 1 the first complex of each pair is normal and the second depicts the block. The QRS interval of the former measures 0.08 second and that of the latter, 0.12 second.

There is a striking similarity between the initial deflections of the two types of complexes in the limb leads and in precordial Leads V_1 , V_4 , V_5 , and V_6 . There is a vast difference, however, between the later QRS components, and this is most pronounced in the leads from the right side of the precordium. When right bundle branch block is present, there is in Lead V_1 a small primary R wave followed by a small downward movement which does not cross the base line, and this in turn is succeeded by a very tall secondary R wave. The normal QRS complex displays a small initial R deflection and a deep S deflection. Both types of complexes undergo the expected transformations in the successive leads of the precordial series.

The paired complexes of Lead V_1 are superimposed in Fig. 2. The white tracing represents complete right bundle branch block and the black one, normal

conduction. The initial deflections of the two complexes are nearly identical in form. The tracings diverge at a point on the descending limb of the initial R wave of the abnormal complex.

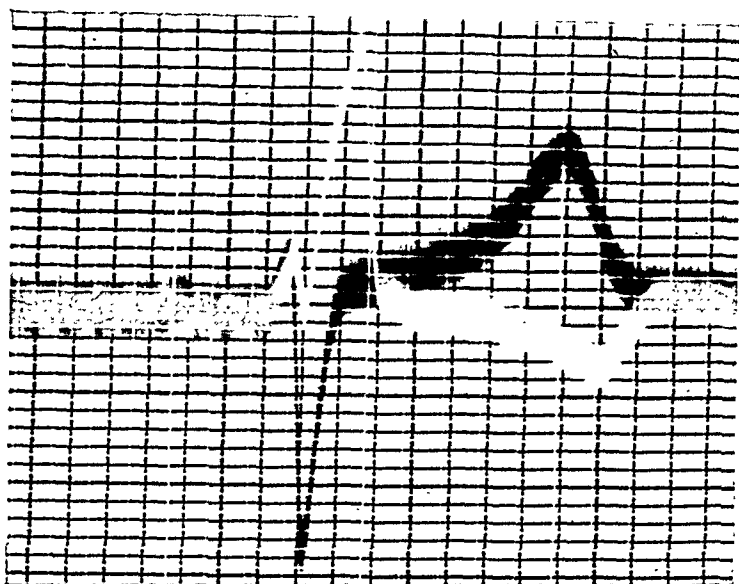


Fig. 2.—The paired complexes of Lead V_1 (Fig. 1) are superimposed.

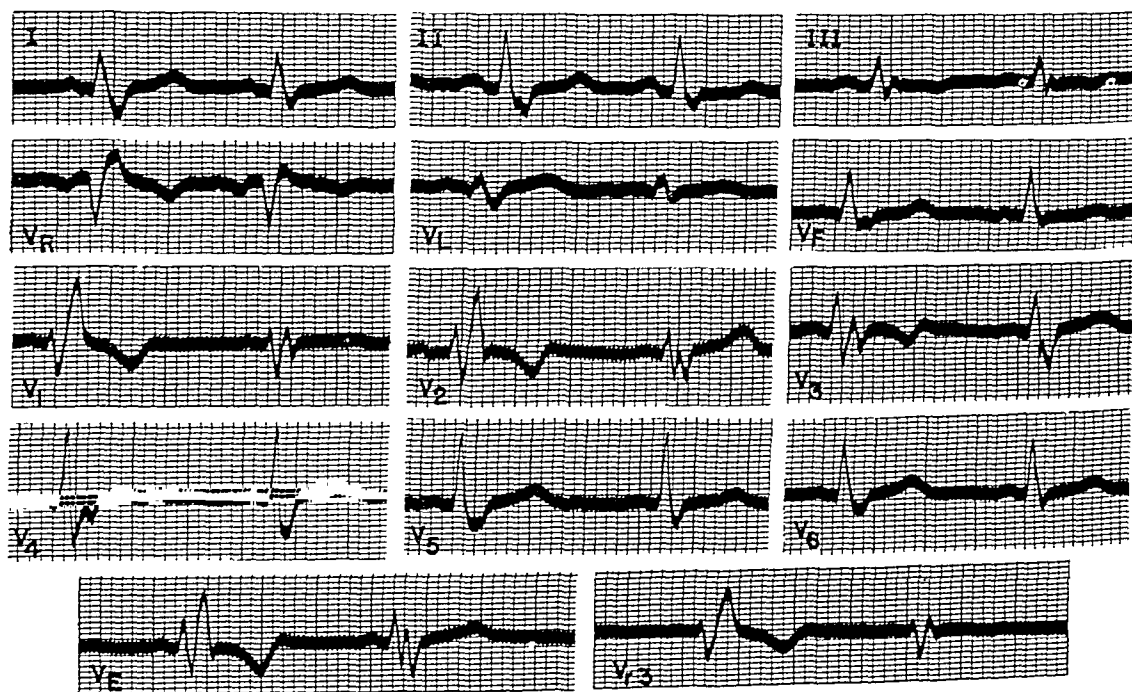


Fig. 3.—The first complex of each pair represents complete, the second incomplete right bundle branch block.

The electrocardiogram reproduced in Fig. 3 is that of a 65-year-old man who was admitted to the University Hospital on Feb. 5, 1941, for the repair of bilateral inguinal hernias. There was a history suggestive of nocturnal dyspnea, but no other complaints referable to the heart were elicited. On physical examination the cardiac border extended 10 cm. to the left of the midline. There were no murmurs, but a presystolic gallop rhythm was heard. The blood pres-

sure was 150/80. Aside from moderate peripheral arteriosclerosis, there were no abnormalities of the cardiovascular system.

The electrocardiogram taken on Feb. 18, 1941, shows complete, alternating with incomplete, right bundle branch block. In Lead I, the first complex, which represents complete block, displays broad W-shaped QRS complexes with a duration of 0.14 second. The QRS complex of the second complex measures only 0.10 second. The initial parts of the paired complexes appeared to be identical in all leads. In the limb leads and in the leads from the left side of the precordium (V_5 and V_6), they differ chiefly with respect to the width of the QRS group and the size of the T deflection. In the leads from the right side of the precordium (V_1 , V_2 , and V_E) and from the right fourth intercostal space in the midclavicular line (V_{R3}), the difference between them is much more pronounced.

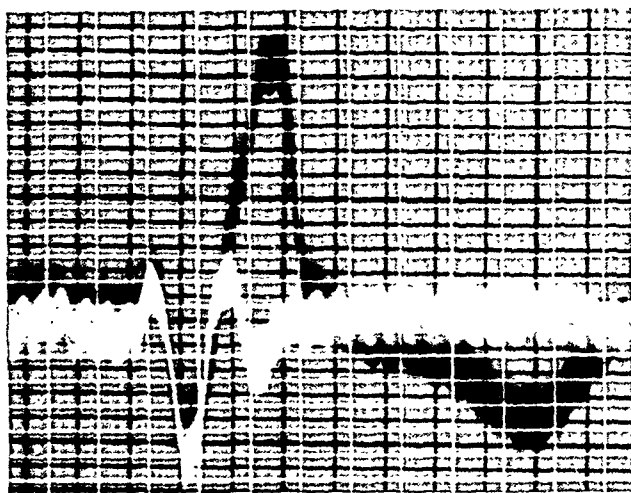


Fig. 4.—The paired complexes of Lead V_1 (Fig. 3) are superimposed.

Note that the R' deflections are much taller in the complexes that represent complete, than in those that represent incomplete right bundle branch block. In Leads V_1 and V_{R3} the R' deflection of the latter is approximately equal to the R wave in height; in Lead V_2 it is smaller than the R wave; and in Lead V_E it is embryonic. There is an orderly sequence of changes affecting the primary and secondary R waves of both complexes corresponding to the step-by-step movement of the exploring electrode from the right to the left side of the precordium as the successive leads were taken. The primary R wave grows taller and finally becomes the early R wave of the leads from the extreme left side of the precordium, whereas the second R deflection becomes gradually smaller and is eventually transformed into an S wave.

It is evident that except for the height of the secondary R deflection the QRS complexes of shorter duration closely resemble in general outline and behavior those which are characteristic of complete right bundle branch block. There can be little doubt that the former represent incomplete right bundle branch block. These complexes are typical of those recorded in the cases which we have placed in Group I, Class a (Fig. 7,A). In Fig. 4 the paired complexes

of Lead V_1 are superimposed. It will be noted that the primary R waves and the downstrokes of the S waves coincide. The divergence begins near the peak of the R' deflection of the complex of shorter duration.

The electrocardiograms reproduced in Figs. 5 and 6 are those of a 59-year-old man who was well until Aug. 23, 1945, when he had a prolonged attack of anginal pain followed by unconsciousness for two hours, and right hemiplegia which persisted for twenty-four hours. Dyspnea and palpitation continued through the following two weeks, at the end of which time the patient was admitted to the University Hospital. Examination revealed moderate cyanosis, a heart rate of 140 per minute with regular rhythm, a blood pressure of 128/80, and a greatly enlarged heart. A Grade 1 blowing systolic murmur was audible in the pulmonic area.

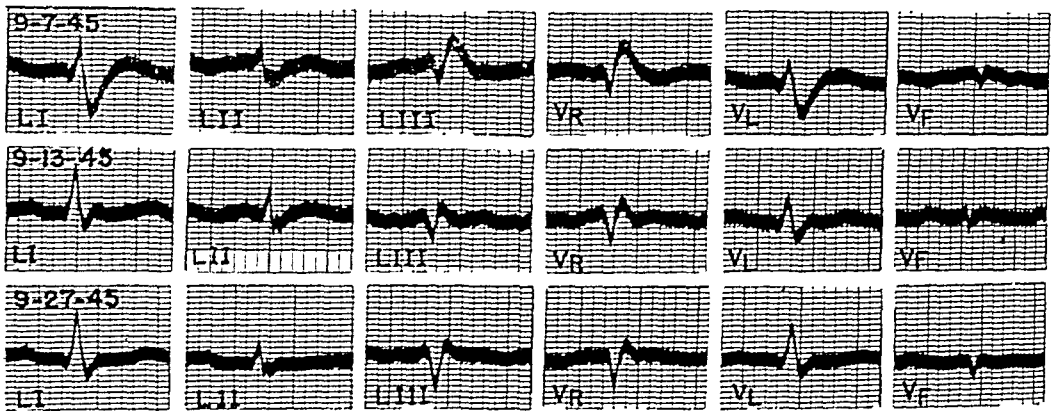


Fig. 5.—Different grades of right bundle branch block in the tracings of a 59-year-old man, who had a prolonged attack of anginal pain followed by transient hemiplegia, cardiac failure, and auricular flutter.

The electrocardiogram taken on Sept. 7, 1945, showed complete right bundle branch block. No distinct P waves were visible in the standard limb leads, but small continuous oscillations, occurring at a rate of 272 per minute, in the leads from the right side of the precordium disclosed the presence of auricular flutter with 2:1 A-V block. In the precordial leads (Fig. 6) the transitional zone is shifted somewhat to the left; compare the complexes of Lead V_4 in this record with those of Lead V_1 in Fig. 8, in which the transitional zone is well to the right. Leads from the left side of the precordium (V_5 and V_6) show early R waves and broad S deflections.

The complexes of the records of Sept. 13, 1945, are similar in outline, but the QRS interval varies considerably in duration. The heart rate is 100 per minute and the grade of A-V block is variable. The QRS complexes change in shape with the length of the preceding diastole. Thus, when the block is 2:1 the QRS interval measures 0.14 second, and when 4:1 block is present this interval measures 0.12 second. In the record taken on Sept. 27, 1945, there is normal sinus rhythm with a heart rate of 94 per minute, and the QRS interval measures 0.11 second. The only other evidence of a conduction defect in the precordial leads of this date is the presence of both an early and a late R deflec-

tion in Lead V_1 . The significance of an R' deflection in Lead V_1 alone, in cases in which there is no other evidence of heart disease, is often open to question. Certainly, in the present instance, this phenomenon appears to represent the residuum of the previously complete right bundle branch block, and therefore a minor grade of incomplete right bundle branch block.

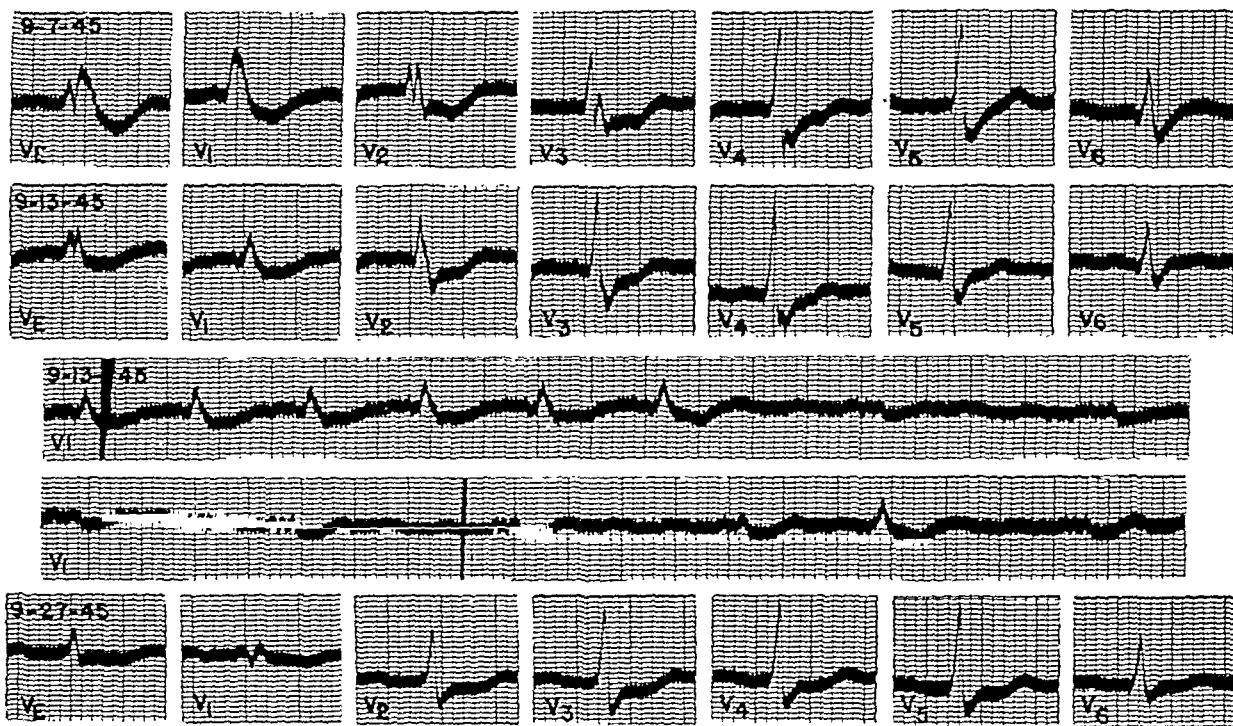


Fig. 6.—The precordial leads corresponding to the limb leads of Fig. 5.

DEFINITION OF INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND THE ORIGIN OF THE QRS DEFLECTIONS IN LEADS FROM THE RIGHT SIDE OF THE PRECORDIUM

The concept of incomplete bundle branch block is based on an analogy. Between complete and permanent A-V block, on the one hand, and slight prolongation of the P-R interval, on the other, there are many conduction defects of intermediate grade. Similar variations in the effects of disease upon the spread of the excitatory process through the bundle branches, which have a structure not unlike that of the main stem of the bundle of His, are to be expected. Complete bundle branch block is now known to be fairly common, and partial bundle branch block, in which normal intraventricular conduction alternates with complete bundle branch block, is by no means rare. The term incomplete bundle branch block is used to designate a delay in the activation of one ventricle due to a defect which slows, but does not interrupt, the transmission of the impulse through the main stem of the bundle branch which supplies this chamber. This

delay cannot exceed that which would be produced by complete block in the same case, but from a theoretical standpoint it may have any lesser magnitude. Practically, it must be great enough to be detectable by the methods available. The term incomplete bundle branch block as defined here excludes defects in conduction affecting the transmission of impulses through some subdivision of a bundle branch but not through the bundle branch as a whole.

Defects in conduction affecting the right branch of the bundle of His cannot alter the time or sequence of the excitation of the muscle normally supplied by the left branch. The electrical forces produced by the activation of this fraction of the myocardium are, therefore, in all respects the same when such defects are present as when they are absent. When there is a delay in the activation of the right ventricle, as much of the QRS complex as is written before excitation of this chamber begins is pure levocardiogram. The earliest part of the QRS complex has the same form in incomplete as in complete right bundle branch block; in both cases, it is of left ventricular origin. Theoretically, it should, then, always be possible when QRS complexes typical of complete right bundle branch block and QRS complexes of shorter duration occur in the same tracing, or same set of tracings, to ascertain whether the latter do, or do not, represent incomplete right bundle branch block, by comparing the initial components of the two types of complexes. In practice the comparison does not always give an entirely unequivocal answer, particularly when it is a question of deciding whether or not the less abnormal complexes depict a minor delay in the activation of all of the right ventricular muscle. The reason lies chiefly, although not solely, in the similarity between the initial QRS component of the complexes which represent complete right bundle branch block and that of those which represent normal intraventricular conduction in the same subject. This similarity is well illustrated by Figs. 1 and 2.

When the excitatory impulse reaches the ventricles by way of the bundle of His and its subdivisions, its direction of spread through each part of the ventricular walls and septum is perpendicular, or nearly perpendicular, to the endocardial surface which bounds it. Four sets of electrical surfaces are generated. Two of these, the forces produced by activation of the right half of the septum and those produced by activation of the free wall of the left ventricle, tend to make the epicardial surface of this chamber and the left side of the thorax positive, and the epicardial surface of the right ventricle and the right side of the thorax negative. The other two, the septal forces of the left ventricle and those produced by the free wall of the right, have the opposite polarity. The forces produced by the right side of the septum tend to make the cavity of the left ventricle positive and that of the right negative, and vice versa. The forces produced by the free walls tend to make both cavities negative. It is clear, therefore, that the QRS deflections always represent a balance of forces directly opposed one to the other.

It has been shown that the potential variations of any point on the precordium are closely related to those of the nearest parts of the epicardial surface.³ The deflections of unipolar leads from the right side of the precordium are ordinarily similar in general outline and in origin to the deflections of unipolar

direct leads from the anterior surface of the right ventricle. One method of analyzing the QRS deflections of direct leads of this kind is to regard them as depicting the electrical forces produced by the part of the ventricular wall in contact with the exploring electrode, measured from a fluctuating base line which represents the potential variations of the adjacent ventricular cavity. In a similar way we may regard the potential variations of the cavity of the right ventricle which occur during a period when its septal wall, but not its free wall, is undergoing activation, as changes in potential produced by the septal muscle plotted upon the time-course of the potential of the left ventricular cavity as reference level. In right bundle branch block the cavity of the left ventricle is negative throughout the QRS interval while that of the right ventricle is initially positive. It is clear that this initial positivity is due to activation of the septum from left to right. Since it occurs before activation of the free wall of the right ventricle has begun, it is transmitted to the epicardial surface of this wall and to the right side of the precordium. An initial R wave in the leads from the right side of the precordium in complete and incomplete right bundle branch block is therefore ascribed to forces produced by the spread of the impulse through the septum from left to right.

When the initial component of QRS has almost exactly the same form when intraventricular conduction appears to be normal as when complete right bundle branch block is present, as in the case illustrated by Figs. 1 and 2, it is difficult to avoid the conclusion that it represents the same phenomenon in both cases. It was shown long ago⁴ that in dogs, leads from the cavity of the right ventricle often display a small initial R deflection indicating that the left side of the septum is activated before the right side. Recently, leads from the cavity of the human right ventricle have demonstrated that this is regularly the case in man.⁵ It is highly probable, therefore, that the resemblance in question is not peculiar to cases of partial right bundle branch block, and that in most, if not all, normal electrocardiograms the initial R wave in Lead V₁ is mainly of septal origin. It can, however, hardly be due to septal forces alone, for this lead displays a small initial R wave in the majority of the cases of left bundle branch block in which this deflection must represent forces produced by activation of the free wall of the right ventricle. When intraventricular conduction is normal, or nearly so, there is no way of estimating in a given instance how much of the initial R wave of Lead V₁, or some other lead from the right side of the precordium, is contributed by forces arising in this wall and how much by forces generated in the septum. The early and rapid development of strong forces, opposed to both of these, in the free wall of the left ventricle makes it hard to ascertain the time-course of those produced by that of the right. These opposing left ventricular forces make the initial R wave of the leads from the right side of the precordium much smaller than it would otherwise be both in right bundle branch block, complete or incomplete, and when no conduction defect is present. It is probable that they are mainly responsible for the distinct separation of the R and R' deflections of the former. It is noteworthy that no similar separation occurs in the leads from the left side of the precordium in left bundle branch block and that in right bundle branch block the early large R wave of these leads is

simultaneous or nearly simultaneous with the cleft between the R and R' waves in the leads from the right side.

In right bundle branch block two of the four sets of forces generated by excitation of the ventricular myocardium are altered with respect to the time of their occurrence, to their polarity, or to both. The forces produced by all or part of the right half of the septum are generated abnormally late in the QRS interval and their polarity is reversed, so that they tend to make both the cavity of the right ventricle and the epicardial surface of this chamber positive instead of negative. The forces produced by the free wall of the right ventricle are delayed still more, but their polarity is not affected. In incomplete right bundle branch block there is no reason to suppose that their magnitude is abnormal or that the order in which the various parts of the free wall of the right ventricle become active is modified. In complete right bundle branch block, however, the contrary is probably the case, for the excitatory impulse reaches the right ventricle by an abnormal route and presumably spreads over the right ventricular muscle in an abnormal fashion. It seems likely that the general course of the impulse from right to left over this muscle gives rise to some electrical forces which are tangential to the inner and outer boundaries of the parts of the wall in which they are generated.⁶ Such forces would tend to make the right side of the precordium more positive than it would be if the order of activation of the different fractions of the free wall of the right ventricle were normal.

It is clear that when the R' deflection is the terminal component of the QRS complex of the leads from the right side of the precordium, the latest part of it must be ascribed to forces produced by late activation of some part of the free wall of the right ventricle. The origin of the earlier fractions of this deflection can only be ascertained with certainty by comparing them with the simultaneous deflections of leads from the cavity of the right ventricle. In canine right bundle branch block, such leads usually display a tiny preliminary upward deflection followed by a moderately tall R wave which is succeeded by an S wave of approximately equal voltage. In epicardial and precordial leads the preliminary deflection is clearly visible, but the main septal R wave is fused with the upward deflection produced by activation of the free wall of the right ventricle to form a broad R' wave, which usually displays on its ascending limb a notch marking the junction of its two components.⁷ We must assume, then, that in human right bundle branch block the earliest part of the R' deflection of the leads from the right side of the precordium is sometimes, if not always, due in part to forces of septal origin.

Consider now the differences between complete and incomplete right bundle branch block and between the different grades of incomplete right bundle branch block with regard to the times of occurrence and magnitudes of the two sets of forces tending to make the right side of the precordium positive during the latter part of the QRS interval. Any abnormal septal forces, due to activation of some part of the right half of the septum from left to right instead of in the opposite direction, which may be present must begin at the same time with respect to the onset of the first QRS deflection, regardless of the grade of the conduction

defect. On the other hand, the magnitude and duration, perhaps only the duration, of these forces must be proportional to the delay in the activation of the right ventricle. The magnitude of the forces produced by the free wall of this chamber may be considerably smaller in incomplete than in complete right bundle branch block, but in all grades of the former it must be the same. The time of occurrence of these forces in the QRS interval, unlike that of the septal forces, measures exactly the grade of the conduction defect. The area of the QRS deflections in any given lead is determined by the direction in which the various parts of the ventricular myocardium are activated and not by the times of their activation.⁸ In right bundle branch block, the change in the area of QRS due to the reversal of the direction in which a part or all of the right half of the septum is activated should be twice as large as the change in area that would be produced by the replacement of this part of the septum by scar tissue. On the other hand, if we disregard the tangential forces mentioned in a previous paragraph, the area contributed to QRS by activation of the free wall of the right ventricle should be the same in all grades of right bundle branch block.

It is not difficult to understand why the R' deflection of the leads from the right side of the precordium is so much smaller in incomplete than in complete right bundle branch block. If the first part of this deflection is of septal origin, we can also understand why its upstroke may begin at the same time in the QRS interval in both cases. In Leads V_1 and V_{r3} of Fig. 3, the R' deflection of the second of the paired complexes begins at the same time and at the same level as that of the first. In Leads V_2 , V_3 , V_4 , and V_E it begins at a slightly higher level and perhaps a trifle earlier in the QRS interval. In all of the leads from the right side of the precordium, the reduction in the grade of the block caused a shift of the apex of the R' wave toward the beginning of the QRS interval greater than the decrease in the length of this interval which it produced (Fig. 4). In Fig. 6 the decrease in the size of the R' deflection in Leads V_1 and V_E as the grade of the block diminished is very striking; in the latter lead this deflection disappeared altogether. The initial R deflection did not change. In Leads V_2 and V_3 the second R wave of the first record shifted toward the beginning of the QRS interval as the grade of the block diminished, for in the later records this deflection is clearly superimposed upon the initial R wave, which has become much taller. Its behavior suggests that it represents forces generated by the free wall of the right ventricle rather than by the septum. It is obvious that the relative magnitude of the septal and free-wall components of the R' deflection may vary greatly from lead to lead. This is in no way surprising.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK VERSUS LOCAL BLOCK

The question arises as to whether it is possible to distinguish with certainty, by means of precordial leads, between incomplete right bundle branch block, as we have defined it, and a defect in conduction located in one of the subdivisions of the right branch of the bundle of His or in the right Purkinje plexus. In the former the intrinsic deflection would be equally delayed in unipolar leads from every part of the right ventricular surface; in the latter this

deflection would be abnormally late only in the leads from that part of the ventricular wall supplied by the subdivision or the part of the plexus, affected. In incomplete right bundle branch block evidence of a delay in the activation of the surface of the right ventricle would, therefore, be expected to appear in all unipolar precordial leads in which the exploring electrode is placed much closer to this surface than to that of the left ventricle. In block affecting a subdivision of the right bundle branch, on the other hand, one would expect to find such evidence in some of these leads, but not in others. It is for this reason that we have classified our cases with respect to the number of leads from the right side of the precordium showing a secondary R wave. We felt, for example, that the evidence pointing to the presence of incomplete right bundle branch block was much stronger when there was a conspicuous R' deflection in both Lead V₁ and Lead V_E, which are from points relatively far apart and presumably reflect the potential variations of quite different parts of the right ventricular surface, than when such a deflection was present in Lead V₁ only. Consequently, the class to which a given electrocardiogram was assigned indicates, in some measure, our opinion as to the probability that it represents incomplete right bundle branch block. When the R' deflection is present in only one precordial lead, the possibility that it is the result of local block, or has some other origin, must be seriously considered. We do not, however, by any means believe that incomplete right bundle branch block can be excluded under these circumstances. It will be noted that in both Fig. 3 and Fig. 6, the number of leads which display an R' deflection is larger when the prolongation of the QRS interval is greater. It seems much more likely that each of these figures represents variations in the grade of a single conduction defect, than that each of them represents two or more distinct conduction defects. The latter possibility cannot, perhaps, be excluded with finality.

It should be pointed out in this connection that although unipolar precordial leads resemble unipolar direct leads in many ways, they differ from them in one important respect. The latter record the potential variations of a single point on the epicardial surface, whereas the former depict a mixture of the potential variations of all parts of the ventricular surfaces in which the potential changes of the nearest parts of this surface are ordinarily the dominant components. It is not necessarily true that the precordial area which yields evidence of delayed activation of the right ventricle when there is a minor delay in the transmission of the impulse through the right branch of the bundle of His will coincide exactly with the precordial area that yields similar evidence when complete right bundle branch block is present. In both cases the size and the location of the area in question are affected by many factors, such as the distance of the anterior wall of the heart from the surface of the precordium, the position of the heart as a whole, and rotation of the heart about its long axis.

THE QRS INTERVAL

In hearts of normal size the free wall of the left ventricle is approximately three times as thick as that of the free wall of the right. If the excitatory impulse spreads through both walls with the same speed, activation of the left

ventricular wall should take much longer than that of the right. The duration of QRS is normally determined, then, by the length of time it takes the excitation process to pass from the endocardial to the epicardial surface of the thickest part of the free wall of the left ventricle. Theoretically, therefore, it is possible in incomplete right bundle branch block of minor degree to have a QRS interval of normal length. In slightly less than one-half of our cases, the QRS interval was less than 0.10 second (Table II), while in the others it was between 0.10 and 0.12 second.

TABLE II. THE QRS INTERVAL

GROUP NO.	LONGEST (SECOND)	SHORTEST (SECOND)	AVERAGE (SECOND)	NUMBER OF CASES		
				0.10 SECOND OR MORE	LESS THAN 0.10 SECOND	TOTAL
I	0.115	0.08	0.099	17	10	27
II	0.115	0.08	0.097	11	9	20
III	0.11	0.08	0.091	8	3	11
IV, A	0.115	0.08	0.105	7	3	10
IV, B	0.11	0.07*	0.087	2	5	7
IV, C	0.10	0.09	0.091	2	4	6
IV, D	0.11	0.09	0.10	3	2	5
V	0.11	0.09	0.099	5	3	8
VI	0.10	0.09	0.095	1	1	2
VII	0.08	0.08	0.08	0	1	1
				55	41	97

*In a child six years old.

At times it is difficult to know with certainty whether an electrocardiogram which displays a QRS interval measuring between 0.10 and 0.12 second represents incomplete or complete right bundle branch block, particularly when the deflections of the leads from the right side of the precordium have a configuration which closely resembles that produced by the latter. Since the QRS duration of some normal electrocardiograms does not exceed 0.06 or 0.07 second, it is quite possible that complete right bundle branch block may sometimes be present when the QRS interval is less than 0.12 second. Clearly, no hard and fast line can be drawn between high grade incomplete right bundle branch block, on the one hand, and complete right bundle branch block, on the other.

CONFIGURATION OF THE COMPLEXES OF THE PRECORDIAL LEADS

The various electrocardiographic patterns considered diagnostic or strongly suggestive of incomplete right bundle branch block are illustrated in Fig. 7. The curves of this figure are arranged from above downward in the order of the groups in which they fall on the basis of the criteria given in an earlier section of this article.

The uppermost row of tracings (A) are the precordial leads of a woman with extensive scleroderma. A previous electrocardiogram, taken on May 24,

1944, was considered to be within normal limits. The tracing reproduced, which was taken on March 29, 1946, shows broad S waves in Lead I, which were not present in the earlier record. The QRS interval is the same in both tracings and measures 0.09 second in the limb leads. There are primary and secondary R

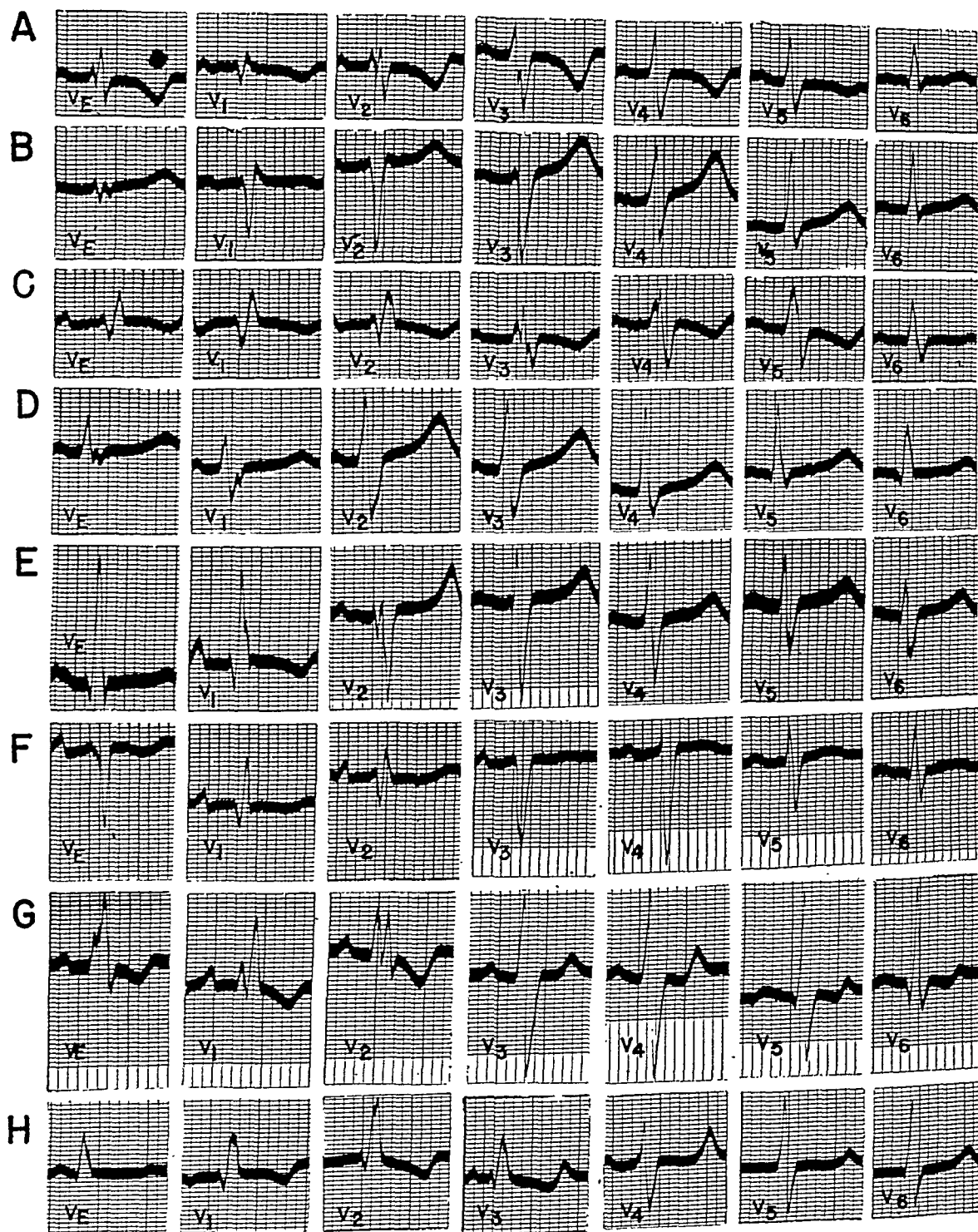


Fig. 7.—Various types of incomplete right bundle branch block (A, B, C, D) and of incomplete right bundle branch block associated with right ventricular enlargement (E, F, G, H).

the apex toward the base. In three of the patients belonging to Group III, additional leads were taken from the right side of the chest (V_{r3} and V_{r4}). These show typical M-shaped QRS complexes of the type usually seen in Lead V_1 in cases of Group I and Group II (Fig. 8).

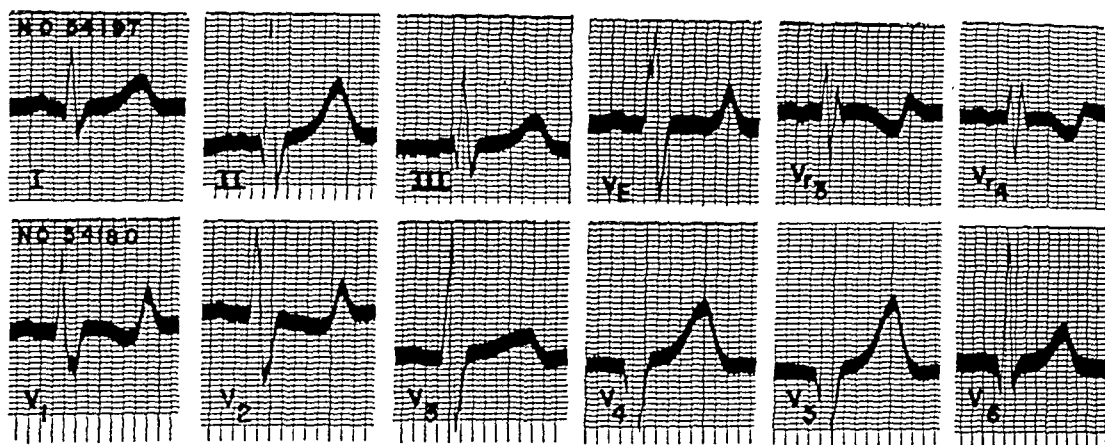


Fig. 8.—Incomplete right bundle branch block with displacement of the transitional zone to the right. Congenital anomaly of the heart (interventricular septal defect) in a girl $3\frac{1}{2}$ years old.

The last four precordial electrocardiograms (*E*, *F*, *G*, and *H* of Fig. 7) are examples of the types found in incomplete right bundle branch block complicated by right ventricular hypertrophy, and are described in a later section.

THE TRANSITIONAL ZONE AND THE VALUE OF ADDITIONAL LEADS FROM THE RIGHT SIDE OF THE CHEST

As we have indicated in the section on classification, the class in which a given electrocardiogram was placed is an index of our opinion as to the probability that it represents incomplete right bundle branch block. It has been pointed out that in incomplete right bundle branch block one would expect to find evidence of late activation of the right ventricle in all of the leads from the right side of the precordium. A localized conduction defect involving the Purkinje network in a limited area, on the other hand, would be expected to affect only those leads in which the exploring electrode was placed directly over the region where activation was delayed. When the expected changes occur in Lead V_1 only (Class *d*) or are confined to Leads V_1 and V_2 (Class *b*), the diagnosis of incomplete right bundle branch block is made with some hesitation. If, however, there is a late R' deflection in both Lead V_1 and Lead V_E , which are from points far apart and must reflect the potential variations of quite different parts of the right ventricular surface, the diagnosis is made with greater confidence.

The main difference between the cases placed in Group III and those of the two preceding groups is that the transitional zone is farther to the right in those placed in Group III, so that the characteristic R and R' waves are not found in the leads from the right side of the precordium. This observation led us to take additional leads from the right side of the chest (V_{r3} , V_{r4} , etc.), and in every case in which they were used, they displayed double R waves of the kind usually

found in Leads V_1 , V_2 , and V_E . Data with respect to the kinds of cases in which such leads were taken are given in Table II. The value of these leads in substantiating the diagnosis of incomplete right bundle branch block is considerable, and it is recommended that they be employed whenever the limb leads and the leads from the right side of the precordium are suggestive, but not diagnostic, of this conduction defect. It must be remembered, however, that the farther the exploring electrode from the surface of the heart, the less accurately does the lead portray the potential variations of the nearest parts of the ventricular surface, and the more difficult is the interpretation of the ventricular deflections. It is conceivable that the leads under consideration may, under some circumstances, lead to an erroneous diagnosis of incomplete right bundle branch block.

There were five cases in Class d and two in Class b in which additional leads from the right side of the chest were taken (Table III). All these showed evidence of late activation of the right ventricle. We have, therefore, considered these cases examples of incomplete right bundle branch block. In the tables there are columns headed "Certain" and others headed "Probable." Under the former heading we have placed the cases of all classes except Class d, plus cases of alternating complete and incomplete right bundle branch block. There may be some question as to the correct diagnosis in the cases of Class b in which no additional leads from the right side of the chest were taken. Because these cases resembled closely those in which such leads supported the diagnosis of incomplete right bundle branch block, and for the purpose of simplifying our classification and discussion, we have placed these cases with those which display more reliable evidence of the presence of this conduction defect.

TABLE III. CASES IN WHICH THE CLINICAL DIAGNOSIS WAS CONFIRMED OR ESTABLISHED BY ADDITIONAL LEADS TO THE RIGHT, CORRELATED WITH THE GROUPS AND SUBGROUPS INTO WHICH THEY WERE CLASSIFIED

GROUP	a	b	c	d	TOTAL
I	3	1	0	1	5
II	1	0	0	1	2
III	0	1	0	4	5
IV, A	2	0	0	0	2
V	1	0	0	0	1
VI	2	0	0	0	2
VII	—	—	—	—	1
Total	9	2	0	6	17

The electrocardiogram reproduced in Fig. 8 is that of a girl $3\frac{1}{2}$ years old. She was studied in the Pediatrics Outpatient Department of the University Hospital in August, 1945, because of anorexia, sleeplessness, and listlessness following an episode of otitis media one month earlier. She was not cyanotic at birth, but a few days later a diagnosis of congenital heart disease was made. Growth and development were about normal. Examination of the heart revealed a diffuse apical impulse. A faint systolic murmur was heard over the

entire precordium, but was loudest in the third and fourth intercostal spaces to the left of the sternum. These findings were considered suggestive of an intraventricular septal defect. The electrocardiogram of Sept. 10, 1945, shows prominent R waves and conspicuous S waves in the three standard limb leads. The QRS interval measures 0.08 second. Lead V_1 displays a rather tall R wave followed by an S wave, in the trough of which there is an embryonic R' wave. Leads V_1 , V_2 , and V_3 exhibit QRS complexes similar to the kind usually found in Leads V_3 and V_4 . They are transitional between those normally found in the leads from the right side of the precordium and the type normally found in the leads from the left side. The transitional zone is, therefore, far to the right. It was not crossed by the standard precordial leads. The leads from the left side of the precordium show a tall R wave preceded by a Q wave and followed by an S deflection. The potential variations of the tip of the ensiform process (V_E) are also of transitional form, and the R peak displays a prominent notch. In order to obtain curves from points to the right of the transitional zone, Leads V_{r3} and V_{r4} were taken. These show double R waves of the kind we have described as indicative of incomplete right bundle branch block. Note the similarity, apart from the duration of the QRS interval, between the complexes of Lead V_1 in the present case and those of Lead V_4 in Fig. 6 (top row), which is one of a series of precordial leads that is characteristic of right bundle branch block, with the transitional zone a little to the left of the usual position. The potential variations of the left leg (V_F) resemble those of the left precordium (V_5 and V_6), while the potential variations of the left arm (V_L) are small. The heart was, therefore, in the semivertical position.

An even more striking example of the influence of the position of the transitional zone upon the configuration of the precordial electrocardiogram in incomplete right bundle branch block is shown in Fig. 9. The patient was a 17-year-old boy who was studied in the Outpatient Department of the University Hospital on April 13 and 14, 1944. He was not blue at birth. When he was one year old his parents noticed that the pulsations of his heart were unusually conspicuous, but the physician who was consulted reassured them. In 1935 the boy was told that he had heart trouble and that he should limit his activity to some extent. Two years previous to the examination at this hospital he had rheumatic fever and was in bed for two months. During this time he had conspicuous cyanosis of the lips and nail beds. Examination of the heart revealed an intense thrill in the pulmonic area and along the left border of the sternum. In the same region there was a Grade V rasping systolic murmur which was transmitted to the left. The heart was not enlarged. There was no cyanosis or acral clubbing. Although there was some uncertainty as to the proper diagnosis, the lesion was thought to be an auricular septal defect or pulmonic stenosis.

The electrocardiogram of April 14, 1944, shows broad S waves in all three standard limb leads. There is a relatively large Q deflection in Lead I. The QRS interval measures 0.09 second. There is a prominent late R wave in Lead V_R . Leads V_1 to V_6 all display QRS complexes of transitional form. Leads V_1 and V_E show a slur on the upstroke of the R wave. Lead V_7 exhibits small complexes with broad S waves; in Lead V_8 the deflections are still smaller, but

of the same general outline. In Lead D_{viii} there are very small primary and secondary R deflections separated by a deep S deflection. The transitional zone in the back lies between Lead V_8 and Lead D_{viii} . Primary and secondary R deflections are present in Leads V_{r8} , V_{r7} , V_{r6} , and V_{r5} , and the configuration of the QRS complex in these leads suggests delayed activation of the right ventricle. There is fusion of the two R waves in Lead V_{r5} . Lead V_{r4} is near the border

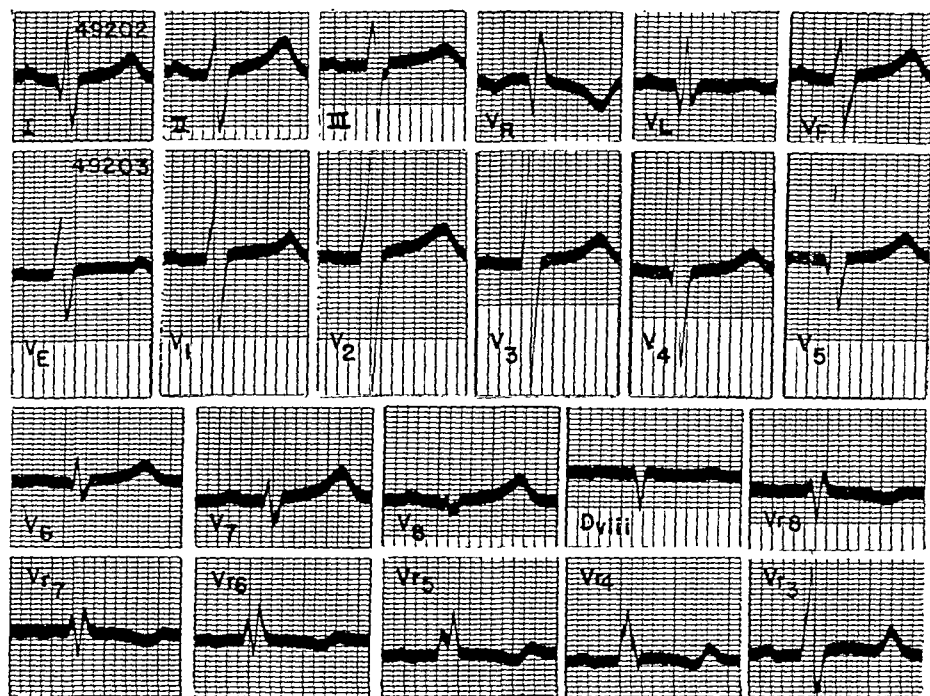


Fig. 9.—Incomplete right bundle branch block in a case of congenital cardiac anomaly (atrial septal defect or pulmonic stenosis). Transitional zone displaced to the right. V_{r3} , V_{r4} , etc., are leads from the right side of the chest corresponding to V_3 , V_4 , etc., from the left side. V_7 is a lead from the left posterior axillary line, V_8 a lead from the left back. D_{viii} is a lead from the eighth dorsal spine.

of the transitional zone in front, and transitional complexes are present in Lead V_{r3} . These tracings display a very broad transitional zone, with extreme displacement of its boundaries to the left and to the right. They illustrate the value of additional leads from points to the right of the right sternal margin when the usual precordial leads fail to cross the transitional zone.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND RIGHT VENTRICULAR HYPERTROPHY

When incomplete right bundle branch block is associated with right ventricular hypertrophy there is characteristically a tall secondary R deflection in the leads from the right side of the precordium. The leads from the left side often show a small R deflection followed by a small S deflection. The pattern is, in general, similar to that seen in right ventricular hypertrophy uncomplicated by incomplete right bundle branch block. Those electrocardiograms

TABLE IV. CORRELATION WITH CLINICAL DIAGNOSIS

	GROUP I		GROUP II		GROUP III		GROUP IV				TOTAL		
	CER- TAIN	PROB- ABLE	CER- TAIN	PROB- ABLE	CER- TAIN	PROB- ABLE	A		B			C	D
							CER- TAIN	PROB- ABLE	CER- TAIN	PROB- ABLE			
Number	16	0	19	2	9	7	1	6	1	3	2		
Males	11	1	1	0	2	1	0	1		3	3		
Females													
Totals	27	1	20	2	11	8	1	7	1	6	5		
Average age	41.5	—	41.1	38.5	47.9	35.0	22.0	28.6	34.0	17.3	33.0		
Males	34.0	64.0	41.0	—	31.0	11.0	—	50.0	—	44.7	37.5		
Females													
Mitral stenosis	4	—	—	—	—	—	—	3	1	2	4	17	
Mitral stenosis plus aortic valvular lesion	5	—	2	—	—	—	—	—	—	1	—	9	
Congenital heart disease	—	—	1	—	—	—	—	—	—	—	—	1	
I. V. septal defect*	1	—	1	—	1	1	—	—	—	—	—	5	
Tetralogy of Fallot	—	—	—	—	—	—	—	1	—	—	—	2	
Lutembacher's syndrome	1	—	—	—	—	—	—	—	—	—	—	2	
Patent ductus arteriosus	—	—	—	—	—	—	—	—	—	—	—	1	
I. A. septal defect†	—	—	—	—	—	—	—	—	—	—	—	1	
Cor pulmonale (chronic)	—	—	—	—	—	—	—	—	—	—	—	2	
Essential hypertension	1	—	2	—	1	1	1	1	—	1	—	9	
Hypertensive heart disease	—	—	1	—	—	—	—	—	—	—	—	3	
Arteriosclerotic heart disease (coronary)*	5	—	—	—	2	—	—	—	—	—	—	3	
Other left-sided lesions	—	—	—	—	1	—	—	1	—	1	—	3	
Heart disease (etiology?)	—	—	1	—	—	—	—	—	—	—	—	1	
Possible heart disease	1	—	—	—	—	—	—	—	—	—	—	1	
Potential heart disease	2	—	2	—	2	2	—	—	—	1	—	8	
No heart disease	5	—	8	2	2	3	—	—	—	—	—	4	
Totals	27	1	20	2	11	8	1	7	1	6	5	20	

*Without myocardial infarction.

†One case in each group had a paroxysmal arrhythmia.

which displayed a tall R' wave in Leads V_1 and V_2 were placed in Group IV (*A, B, C, and D*). The various QRS configurations encountered are illustrated in Fig. 7 (*E, F, G, and H*). In addition to changes suggestive of incomplete right bundle branch block, all of these patients showed definite right axis deviation in the limb leads. With one exception the clinical diagnoses made were consistent with the presence of right ventricular hypertrophy (Table IV).

A precordial electrocardiogram which is representative of Group IV, A is reproduced in Fig. 7, *E*. It was taken on Nov. 20, 1945. The patient was a man 22 years of age with physical signs typical of the tetralogy of Fallot. The standard limb leads show right axis deviation and large P waves in Lead II. The unipolar extremity leads indicate that the heart was in the vertical or semivertical position. Leads V_1 and V_E display a small initial R wave and a very tall R' deflection. The leads from the left side of the precordium, and

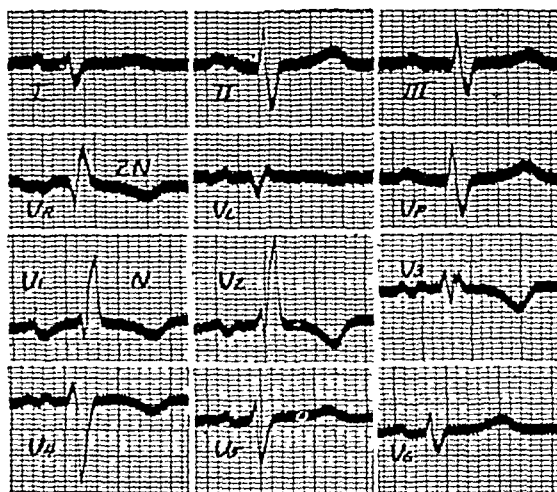


Fig. 10.—Incomplete right bundle branch block associated with right ventricular enlargement. The patient was a 42-year-old man with rheumatic mitral stenosis and aortic regurgitation. Note large secondary R waves in Leads V_1 and V_2 .

especially Lead V_6 , show smaller QRS deflections, with R and S waves of nearly equal size. In this particular instance the transitional zone begins with Lead V_2 ; it is not uncommon to find this zone displaced somewhat to the right in cases of the kind under consideration. The pattern is the reverse of that seen in incomplete right bundle branch block without right ventricular hypertrophy, with regard to the size of the R' wave in the leads from the right side of the precordium in comparison with that of the R wave in the leads from the left side.

Another example of the tracings placed in Group IV is reproduced in Fig. 10. This electrocardiogram is that of a man, 42 years of age with rheumatic heart disease, mitral stenosis, and aortic regurgitation. Roentgenographic examination, including orthodiagraphy, showed cardiac enlargement, left auricular

enlargement, and calcification of the mitral valve. Large deformed P waves suggestive of auricular enlargement and consistent with the diagnosis of mitral stenosis are present in Leads I and II. The P-R interval measures 0.21 second and the QRS interval, 0.08 second. There are large S waves in Leads I, II, and III, and a broad, late R wave in Lead V_R . Since the potential variations of the left leg resemble those of the left side of the precordium, and the deflections of Lead V_L are small, the heart was in the semivertical position. Leads V_1 and V_2 show a small initial R wave followed a very tall R' deflection. The latter is a little larger in Lead V_2 than in Lead V_1 . The leads from the left side of the precordium (V_5 and V_6) display rather small QRS deflections with rather broad S waves. The other precordial leads (V_3 and V_4) exhibit complexes transitional in form between those found in the leads from the right, and those found in the leads from the left side of the precordium. The large secondary R wave in the leads from the right side diminishes rather rapidly in the leads from points farther to the left, and there is no sign of it in Lead V_4 . This is a fairly typical example of the pattern seen in the precordial leads when incomplete right bundle branch block is associated with right ventricular hypertrophy.

The electrocardiogram reproduced in Fig. 7, *F* was taken on Feb. 16, 1943. The patient was a man 35 years of age who had suffered since infancy from a chronic cough productive of foul sputum. There was a history of several attacks of "pneumonia" during the six years previous to the examination, and of increasingly severe dyspnea, upper abdominal pain, and slight edema of the ankles during the two weeks preceding the examination. His general health had been poor. Roentgenographic examination of the chest revealed widespread, patchy pneumonitis, perihilar infiltration, and thickening of the pleura at both apices. These findings were considered highly suggestive of bronchiectasis. The heart was moderately enlarged. The blood pressure was 110/74. Clubbing of the fingers and toes and obvious acral cyanosis were present. The patient did not return for further studies.

The electrocardiogram shows slight right axis deviation, and unusually large P waves and inverted T waves in Leads II and III. The QRS interval measured 0.08 second in the limb leads. Leads V_1 and V_2 show double R waves, indicating a delay in activation of the right ventricle. The R' deflection is relatively tall in Lead V_1 and measures about 9.5 millimeters. Lead V_E shows a small initial R wave followed by a deep S deflection. The complexes of Lead V_2 are transitional in form between those of Lead V_1 and those of Lead V_3 . The QRS complexes of the midprecordial leads (V_3 and V_4) are of unusual outline in that they consist of a small R wave followed by a deep S deflection, while those of Lead V_5 appear to be transitional in form between the complexes of Lead V_4 and those of Lead V_6 . The R wave of the latter is only slightly smaller than the R' deflection of Lead V_1 and is followed by a prominent S wave.

Some of the features seen in this tracing are rather difficult to explain satisfactorily. The leads from the right side of the precordium are rather strongly suggestive of incomplete right bundle branch block, and the tall R' deflection in Lead V_1 , together with the clinical impression of cor pulmonale, makes it highly probable that a right ventricular hypertrophy was present. The factors re-

sponsible for the QRS pattern seen in the midprecordial leads are not obvious, but this configuration indicates that the main electrical forces acting on the midprecordium had an anteroposterior direction. It seems probable that this pattern is the result of some peculiarity in the position of the heart which led to an unusual distribution of the areas on the surface of the chest to which the potential variations of the two ventricular surfaces were transmitted. It may be mentioned in this connection that the leads from the extreme right side of the precordium are from points relatively near the thick basal parts of the right ventricular wall, whereas those from the midprecordium are from points closer to the thinner central and apical parts of this wall. In animals, leads from the base of the right ventricle show large R waves, while those from the central region and apex show small R waves. It is possible that under some circumstances the precordial leads may be affected in the same way.

The tracing reproduced in Fig. 7, G is an example of those placed in Group IV, Class c. The patient was a 9-year-old boy who at the age of 7 had begun to tire easily, to become dyspneic, and to develop anorexia. There was no known episode of acute rheumatic infection. When he was 8 years old, a cardiac murmur was discovered. A few months later edema of the ankles developed, and during the following two weeks he was orthopneic. Two months prior to hospital admission, ascites, sufficient in amount to require two paracenteses, appeared, and was accompanied by nocturnal dyspnea. On examination, the heart was found to be greatly enlarged both to the right and to the left. A loud systolic and a rumbling diastolic murmur were heard at the apex, and there was a rather faint, short diastolic murmur along the left edge of the sternum. The blood pressure was 120/40. An orthodiagram and film studies of the chest showed generalized cardiac enlargement with a moderate degree of pulmonary congestion. There was pronounced diminution of the retrocardiac space as well as deformity of the anterior thoracic wall as a result of tremendous cardiac dilatation. The diagnosis was rheumatic heart disease, mitral stenosis, and aortic regurgitation, but the possibility of the presence of an interatrial septal defect could not be excluded.

The electrocardiogram taken on June 7, 1945, shows right axis deviation and a QRS interval of 0.10 second in the limb leads. The P waves are unusually large and broad and suggest auricular enlargement. The leads from the right side of the precordium (V_1 and V_2) and from the tip of the ensiform process (V_E) display complexes of the kind we have described as characteristic of incomplete right bundle branch block plus right ventricular hypertrophy. The transition from complexes of the kind seen in the first to complexes of the kind seen in the last leads of the precordial series begins with Lead V_2 and ends with Lead V_5 . Lead V_6 shows a very tall R wave, which, again, is an unusual feature not easily explained.

The last set (H) of precordial leads in Fig. 7 is a representative of Group IV, d. The patient was a 35-year-old man who was studied at the University Hospital in December, 1943. During the preceding three years he had had several episodes of hemoptysis following strenuous exertion. He had been a "blue baby" and for many years his friends had commented on his blue color,

and particularly on his blue-black lips. From childhood he had become purple on moderate exertion. He had been told on several occasions that there was something wrong with his heart, and had had clubbing of the fingers and toes as long as he could remember. Examination revealed moderate acral cyanosis. The precordial area was prominent. The heart was moderately enlarged to the left. At the apex there was a loud, low-pitched, coarse diastolic murmur ending in a snapping first sound. There were variations in the intensity of this sound. Along the left border of the sternum there was a faint, high-pitched diastolic murmur. The blood pressure was 104/70. The hemoglobin was 142 per cent. Roentgenographic examination showed pronounced enlargement of the pulmonary conus and the pulmonary vessels. The increase in the size of these vessels was so great as to lead to a suspicion of aneurysm of the pulmonary artery. There was also transposition of the thoracic aorta. The heart was moderately enlarged in all diameters, but there was no evidence of atrial enlargement. The proper anatomic diagnosis was thought to be interatrial septal defect.

The electrocardiogram of Dec. 20, 1943, revealed that from time to time idioventricular rhythm was present, and that the rate of this rhythm was fast enough to cause A-V dissociation. This accounts for the variations in the position of the P wave in the illustration. Leads V_E , V_1 , and V_2 were taken with the electrocardiograph operating at its normal sensitivity; the other precordial leads were taken with the instrument at one-half the normal sensitivity. The QRS interval measures 0.08 second in the limb leads. The leads from the right side of the precordium (V_1 and V_2) show small initial R deflections and tall R' waves similar to those we have described as characteristic of this group. The same QRS configuration is present in Lead V_3 , and a remnant of the primary R can be seen at the base of the main upward deflection in Lead V_4 . Besides a slight shift of the transitional zone to the left, the sequence of changes suggests that the secondary R wave moved toward the beginning of the QRS group and engulfed the primary R wave as the exploring electrode was moved from right to left. The leads from the left side of the precordium display a prominent early R deflection followed by a conspicuous S wave. The transitional zone is not well defined, but the late R wave of Leads V_1 , V_2 , and V_3 is replaced by an S deflection in Leads V_4 , V_5 , and V_6 .

The factors responsible for the large R' deflection in the leads from the right side of the precordium in incomplete right bundle branch block associated with right ventricular hypertrophy are no doubt the same as those that give rise to the abnormally large QRS deflections both in uncomplicated hypertrophy of the left and in uncomplicated hypertrophy of the right ventricle. In attempts to explain these abnormally large deflections it has been suggested that: (1) Because the solid angle subtended at the exploring electrode by the extensive surface area of the hypertrophied ventricle is abnormally large, the effect of the enlarged ventricle upon the potential variations of this electrode is much the same as if it were moved closer to the epicardial surface. (2) In ventricular hypertrophy the cross-sectional area of each individual muscle fiber is increased. Increasing the cross-sectional area of a muscle fiber reduces its internal resistance, but leaves unchanged the external resistance in the circuits involved in excitation.

Since the voltage drop in each part of the circuit is proportional to the ratio of the resistance of that part to the total resistance in the circuit, the effect of increasing the size of the fiber is to increase the magnitude of the potential variations over its external surface produced by the spread of the excitatory process.

Probably the increased voltage of the electrocardiographic deflections in ventricular hypertrophy is due to a combination of several factors. When incomplete right bundle branch block is associated with right ventricular hypertrophy, the increased voltage developed during activation of the free wall of the right ventricle, and perhaps during activation of the right half of the septum also, gives rise to the very tall secondary R wave recorded in the leads from the right side of the precordium.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND LEFT VENTRICULAR HYPERTROPHY

In four of the cases of right bundle branch block which we studied, it was thought that the defect in conduction was complicated by electrocardiographic signs suggestive of left ventricular hypertrophy. There was one case of coarctation of the aorta (not included in our series of cases of incomplete right bundle branch block) in which the QRS interval measured 0.12 second. We suspected that in this instance incomplete right bundle branch block was associated with hypertrophy of the left ventricle. Since both the delay in conduction and the increased thickness of the free wall of the left ventricle would contribute to the duration of the QRS interval, it may be assumed that had the hypertrophy not been present the QRS interval would have been shorter. The electrocardiogram shows significant left axis deviation, and the heart was in the semihorizontal electrocardiographic position. The leads from the right side of the precordium show two R waves of rather small and nearly equal voltage, separated by a very deep S deflection. Those from the left side exhibit abnormally tall R waves and inverted T waves. The leads from the midprecordium display deflections of transitional form. In other words, the pattern is similar to that seen in left ventricular hypertrophy, apart from the evidence of delayed activation of the right ventricle.

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK ASSOCIATED WITH MYOCARDIAL INFARCTION OR WITH PULMONARY EMBOLISM

There were eleven cases in our series in which myocardial infarction had occurred. The sex distribution, types of infarcts, and other data are given in Table V. There is comparatively little difference, with regard to the configuration of the ventricular deflections of the electrocardiogram, between incomplete right bundle branch block associated with infarction and complete right bundle branch block associated with infarction. The latter has been discussed in detail by Rosenbaum and others.^{7,9} Posterior infarction is recognized by the characteristic changes which it produces in Leads II, III, and V_F. Anteroseptal infarcts abolish the primary R wave in the leads from the right side of the pre-

cordium, but the R' wave is unusually large in these leads because of the reduction of the opposing left ventricular forces incident to the infarction.

There were two cases in which incomplete right bundle branch block was associated with pulmonary embolism. They are mentioned here for the sake of completeness. These cases will be discussed in detail in a subsequent article.

TABLE V. INCOMPLETE RIGHT BUNDLE BRANCH BLOCK AND MYOCARDIAL INFARCTION

	CERTAIN	PROBABLE
Number		
Males	7	3
Females	1	0
Total	8	3
Average age		
Males	51.6	54.3
Females	59.0	—
Anteroseptal infarct	4	0
Extensive anterior infarct	2	0
Small anterior infarct	1	0
Posterior infarct	1	3
Total	8	3

CORRELATION OF ELECTROCARDIOGRAPHIC AND CLINICAL DATA

Table VI gives the age and sex incidence of incomplete right bundle branch block in our series of cases. It will be noted that the incidence is relatively high in the first decade of life. This is obviously due to the frequency of this conduction defect in congenital heart disease. In the second decade the number of cases is smaller, but thereafter it rises gradually, and the greatest frequency occurs in the fourth, fifth, and sixth decades. There is a preponderance of males over females in the ratio of approximately 3:1.

TABLE VI. INCIDENCE ACCORDING TO DECADES

DECADE	MALES	FEMALES	TOTAL
First	10	1	11
Second	3	3	6
Third	8	4	12
Fourth	18	4	22
Fifth	8	5	13
Sixth	13	8	21
Seventh	9	0	9
Eighth	2	1	3
Totals	71	26	97

Number of cases, 96.
Highest age, 79 years.

Lowest age, 19 months.
Average age, 40.8 years.

Average age in females, 41.7 years.
Average age in males, 39.9 years.

Table IV gives the distribution with respect to clinical diagnosis, sex, and age of the patients included in the first four groups. This table has been referred to previously in connection with the discussion of incomplete right bundle branch block associated with right ventricular hypertrophy.

It is interesting to note that twenty of the patients showed no evidence of heart disease. In eight additional instances a diagnosis of possible heart disease, and in four more a diagnosis of potential heart disease was made. There were also three cases of essential hypertension in which evidence of cardiac involvement was not elicited. Consequently, there were in all, thirty-one cases in which a definite diagnosis of heart disease could not be made. It is, therefore, hazardous to make a clinical diagnosis of heart disease on the basis of the electrocardiographic findings alone in cases in which the only demonstrable abnormality is incomplete right bundle branch block. On the other hand, the remaining patients had serious heart disease. There were forty-seven with lesions involving the right and thirteen with lesions involving the left side of this organ.

DISCUSSION AND CONCLUSIONS

Since most of our material has been discussed as it has been presented, there is little need for further emphasis on the great majority of points, except to indicate what we consider the criteria necessary for diagnosis.

Incomplete right bundle branch block should be suspected in every case in which there is a relatively broad S wave in Lead I, especially if the QRS interval is longer than in the average normal electrocardiogram. In our cases of incomplete right bundle branch block the QRS interval ranged from 0.08 to 0.115 second.

The presence of a primary and a secondary R wave or a prominent late R wave in Lead V_R is relatively common in cases of incomplete right bundle branch block, but is also frequent when this conduction defect is not present and is not a reliable sign.

The presence of an early R deflection and a late R' deflection in the leads from the right side of the precordium, especially if both deflections are present in both Lead V_1 and Lead V_E , is diagnostic. If suggestive changes are present in Lead V_1 , or in Leads V_1 and V_2 , it is advisable to take additional leads from the right side of the chest (V_{r3} and V_{r4}) or to carry out an even more extensive exploration of the heart field in order to confirm the diagnosis.

When right ventricular hypertrophy and incomplete right bundle branch block are associated, there is, in addition to the changes described, a very tall R' deflection in the leads from the right side of the precordium. This deflection usually exceeds 10 mm. in height. The leads from the left side of the precordium often show rather small R deflections and deep S waves. However, electrocardiograms representing this combination may exhibit a variety of patterns. Four of these have been described.

REFERENCES

1. Rothberger, C. J., and Winterberg, H.: Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens; *Ztschr. f. d. ges. exper. Med.* 5:264, 1917.
2. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* 8:230, 1921.
3. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Olivera, R., Scarsi, R., and Barker, P. S.: The Pre-cordial Electrocardiogram, *AM. HEART J.* 27:2, 1944.
4. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Interpretation of the Galvanometric Curves Obtained When One Electrode is Distant From the Heart and the Other Near or in Contact With Its Surface. II. Observations on the Mammalian Heart, *AM. HEART J.* 10:176, 1934.
5. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiograms Obtained by Heart Catheterization, *AM. HEART J.* 33:604, 1947.
6. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, *AM. HEART J.* 6:5, 1931.
7. Rosenbaum, F. F., Erlanger, H., Cotrim, N., Johnston, F. D., and Wilson, F. N.: The Effects of Anterior Infarction Complicated by Bundle Branch Block Upon the Form of the QRS Complex of the Canine Electrocardiogram, *AM. HEART J.* 27:783, 1944.
8. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, *AM. HEART J.* 10:46, 1934.
9. Wilson, F. N., Rosenbaum, F. F., Johnston, F. D., and Barker, P. S.: The Electrocardiographic Diagnosis of Myocardial Infarction Complicated by Bundle Branch Block, *Arch. d. Inst. de Cardiol. de Mexico.* 14:3, 1945.

VARIABILITY OF THE ELECTROCARDIOGRAM IN NORMAL YOUNG MEN

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INTRODUCTION

IN THE proper clinical interpretation of electrocardiograms, quantitative criteria of normality are essential, but the values generally used have been arrived at without adequate sampling and detailed statistical analysis. Recently, new data on larger groups of persons have shown that the ranges for many electrocardiographic items in apparently normal persons are greater than had been supposed.^{1,2} The diagnosis of such marked pathologic changes as intraventricular block, infarcts, or advanced degrees of preponderance is not called in question, but it is clear that progress in the use of electrocardiography for the evaluation of less extreme abnormalities requires a quantitative approach based on exactly defined standards. Such an approach should take into account not only the differences between individuals but also the fluctuations within individuals. The day-to-day variability of the electrocardiographic complexes is the focus of the present study. This aspect is especially important for a more precise interpretation of borderline electrocardiograms. In addition, the lability of the electrocardiographic complexes as characterized by the size of the day-to-day fluctuations may constitute a new criterion of abnormality, even when the fluctuations occur within the so-called normal limits.

In a thorough search of the literature we failed to find any data on day-to-day variability of the electrocardiogram except an early communication by Lewis.³ At that time the electrocardiogram was taken with the patient in a sitting position, and many items are not exactly comparable with later material. Lewis,^{3,a} while recognizing that the electrocardiographic complexes exhibit considerable differences among healthy individuals, considered the electrocardiogram as essentially constant for a given individual and suggested that it might be adopted as a means of individual identification. He did not analyze the material statistically.

The absence of data on intraindividual variability is surprising in view of the widespread clinical use of electrocardiography. This absence might be explained by

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This work was made possible, in part, by a grant from the United States Public Health Service, recommended by the Cardiovascular Study Section.

the present use of the normal range limits as criteria, which implies that the knowledge of intraindividual variability within the normal range is irrelevant for clinical interpretation; and by the tradition, since Einthoven and Lewis, of regarding the electrocardiogram in "normal" subjects as practically constant. Both concepts are basically incorrect.

Knowledge of intraindividual variability is essential for the effective use of serial electrocardiography in patients. Such a dramatic development as healing of a myocardial infarct will probably overshadow completely the magnitude of intraindividual variability, but comparatively minor changes are often interpreted as improvement or deterioration. This cannot be safely done without knowledge of the amount of variation to be expected by "chance" alone in repeated electrocardiograms.

In the present communication, data on the consistency of electrocardiographic complexes in a comparatively small but well-controlled group will be given, together with an analysis of the various sources of variability.

METHOD

Three standard and three chest leads (CF_1 , CF_2 , and CF_4) were taken on eleven occasions in the basal condition on each of twelve subjects. The location for the placement of the chest electrode was marked by intracutaneous dye injection. The repeated tests were made at intervals of three to eleven days. The whole experimental period was about two months. The dye spots were visible throughout this period. Simultaneously with the electrocardiogram, the heart sounds were recorded during arrested respiration. The interval from the first to the second heart sound was measured as the duration of mechanical systole (systole). In addition, the following intervals were measured: R-R, P-R, QRS, and Q-T. The R-R interval, Q-T interval, and duration of mechanical systole were averaged from five beats, usually in Lead II. The value K, obtained by dividing through $\sqrt{R-R}$, was calculated both for Q-T, (K_{QT}), and for the duration of mechanical systole ($K_{systole}$).

The difference between the longest and shortest R-R interval in any given electrocardiogram was used as a criterion of arrhythmia (Δ Max.-Min. R-R). The amplitudes of the P waves, the QRS complex, RS-T segments, and T waves were measured in all leads in terms of standardized millimeters, 10 mm. equalling 1 millivolt. In addition to the standard deflection incorporated in the electrocardiograph (Sanborn), an external calibration source was applied.

The axis of QRS and the axis of T were calculated by the use of Dieuaide's procedure. Since the same subjects were tested repeatedly, the usual clinical method for estimation of the over-all magnitude of the QRS complex as the sum of the amplitudes in Leads I, II, and III (Σ_{QRS}), appeared to be sufficient. A similar procedure was used for the T waves (Σ_T). The quotient R/S was calculated for CF_1 , CF_2 , and CF_4 .

The subjects were twelve healthy young men, between 20 and 30 years of age. They received a thorough physical examination before the start of the

experiments. In addition to the clinical routine examination, the response to exercise, heat exposure, and vertical position was tested and found to be normal. Their diet and daily routine during the experimental period was known; major emotional, physical, or nutritional interference during the experimental period could be excluded.

Statistical Procedures.—The methods of statistical analysis used here have been presented in detail previously.⁴ The essential task is to determine the portion of the variability of measured electrocardiographic complexes which can be attributed to differences between individuals, day-to-day physiological fluctuation in the electrocardiographic functions, and the error of measurement.

Variation in the electrocardiographic complexes, determined for n individuals on k days, can be expressed in terms of differences arising from three sources: (1) The difference between a value (Y_{ID}), obtained for a given individual (I) on a given day (D), and the mean of all values obtained for the given individual ($Y_{ID} - \bar{Y}_I$). (2) The difference between Y_{ID} and the mean (\bar{Y}_D) of the values obtained for all the individuals on a given day ($Y_{ID} - \bar{Y}_D$). (3) The difference between Y_{ID} and a predicted value, \hat{Y}_{ID} ; i. e. ($Y_{ID} - \hat{Y}_{ID}$). The latter value is based on the grand mean of the determinations on all the individuals on all the days (\bar{Y}), the difference between an individual's mean and the grand mean, ($\bar{Y}_I - \bar{Y}$), and the difference between a day's mean and the grand mean, ($\bar{Y}_D - \bar{Y}$); $\hat{Y}_{ID} = \bar{Y} + (\bar{Y}_I - \bar{Y}) + (\bar{Y}_D - \bar{Y})$.

The sums of squared differences, divided by the appropriate "degrees of freedom," are referred to as variances (or "mean squares"). Using the symbols defined, we obtain three variances:

Variance "within days," V_{wD} , indicating the magnitude of the subject-to-subject (interindividual) variation;

$$(1) \quad V_{wD} = \frac{\frac{nk}{I} \sum (Y_{ID} - \bar{Y}_D)^2}{k(n-1)}$$

Variance "within individuals," V_{wI} , representing the magnitude of day-to-day (intraindividual) variation:

$$(2) \quad V_{wI} = \frac{\frac{nk}{n} \sum (Y_{ID} - \bar{Y}_I)^2}{n(k-1)}$$

"Random" variance, V_R , measuring the "random" variation in the scores:

$$(3) \quad V_R = \frac{\frac{nk}{(n-1)(k-1)} \sum (Y_{ID} - \hat{Y}_{ID})^2}{(n-1)(k-1)}$$

The formulas (1) to (3) indicate the theoretical derivation of the variances. In carrying out the actual computations the procedures can be greatly simplified (see Brozek and Alexander⁴).

In evaluating the day-to-day fluctuations in the scores obtained in repeated determinations, the intraindividual variance (V_{wI}) is to be compared with the interindividual variance (variance "within days," V_{wD}).

We may use either a percentage expression:

$$(4) \quad \% V_{wI} = \frac{100 V_{wI}}{V_{wD}} \text{ or}$$

relate the two values in the form of a coefficient of day-to-day consistency:

$$(5) \quad r'_c = 1 - \frac{V_{wI}}{V_{wD}}.$$

In cases where V_{wI} is significantly larger than V_R , as indicated by the ratio V_{wI}/V_R , the random variance must be used as the measure of the chance variation in the scores. Again, it may be related to V_{wD} in the form of a percentage:

$$(6) \quad \% V_R = \frac{100 V_R}{V_{wD}}, \text{ or}$$

of a coefficient of consistency:

$$(7) \quad r_c = 1 - \frac{V_R}{V_{wD}}$$

Using the percentage relationship, complete absence of consistency would be indicated by 100 and complete consistency would be indicated by zero. With the variances expressed in terms of a coefficient of consistency, a value of 0.0 indicates complete absence of consistency and a value of 1.0 complete consistency.

So far, the variance within individuals (V_{wI}) has been considered as a uniform source of variability. However, it may be assumed that V_{wI} consists of two parts: (1) the variation due to true day-to-day changes in the electrocardiographic characteristics, estimated as the corrected variance within individuals, *corr.* V_{wI} ; (2) the variation due to the error in measuring the records, determined as V_{wM} , the variance within measurements. We assume further that these two variances are additive:

$$(8) \quad V_{wI} = \text{corr. } V_{wI} + V_{wM}.$$

In order to separate these two sources of intraindividual variation, the electrocardiographic records obtained from the group on one day were independently remeasured three times at intervals of several weeks. All measurements were made by the same person, who had had considerable experience in this task. In computation, V_{wM} is obtained in the same way as V_{wI} , except that it is based on repeated measurements of the same set of records rather than on electrocardiographic determinations made on different days.

TABLE I. MEANS, STANDARD DEVIATIONS (INTERINDIVIDUAL, INTRINDIVIDUAL, AND ERROR OF MEASUREMENT), AND 90 PER CENT RANGE OF ELECTROCARDIOGRAPHIC ITEMS; LIMB LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

	MEAN	INTERINDIVIDUAL		INTRINDIVIDUAL		ERROR OF MEASUREMENT		ACCEPTED NORMAL LIMITS
		S.D.	90% RANGE (±)	S.D.	90% RANGE (±)	S.D.	90% RANGE (±)	
Intervals, in 1/100 sec.								
1. R-R	106.9	13.23	21.8	8.59	14.10	0.288	0.474	60 to 100
2. ΔMax.-Min. R-R	8.9	6.90	11.3	5.40	8.90	0.736	1.210	
3. P-R	14.7	2.33	3.8	0.854	1.40	0.612	1.010	12 to 21
4. QRS	7.2	1.31	2.2	0.400	0.66	0.354	0.582	6 to 10
5. KQT	0.394	0.021	0.035	0.015	0.025	0.007	0.012	0.34 to 0.43*
6. Ksyst.	0.326	0.017	0.028	0.011	0.018	0.005	0.008	
Amplitudes, in mm. (1 mm. = 0.1 mv.)								
1. P ₂	1.04	0.243	0.40	0.141	0.23	.050	.082	0.3 to 2.5†
2. R ₁	5.05	1.98	3.30	0.548	0.90	.097	.160	1.5 to 14†
3. R ₂	12.81	4.28	7.00	0.640	1.10	.130	.214	4.0 to 23†
4. R ₃	8.97	5.26	8.70	0.825	1.40	.224	.368	1.0 to 20†
5. Σ _{QRS}	29.16	8.73	14.40	1.490	2.50	.329	.541	
6. RS-T ₁	0.11	0.17	0.28	0.152	0.25	.110	.181	-0.5 to 2.0†
7. RS-T ₂	0.11	0.20	0.32	0.182	0.30	.084	.138	-0.5 to 2.0†
8. RS-T ₃	0.14	0.24	0.39	0.155	0.25	.100	.164	-1.0 to 2.0†
9. T ₁	2.92	0.91	1.50	0.387	0.64	.089	.146	0.4 to 5.0†
10. T ₂	3.83	1.79	2.90	0.439	0.72	.110	.181	0.1 to 6.5†
11. T ₃	1.51	1.14	1.90	0.443	0.73	.114	.188	-1.3 to 4.3†
12. Σ _T	8.25	3.27	5.40	0.814	1.30	.158	.260	
Axis								
1. QRS axis°	69.20	16.52	27.20	6.560	10.80	1.740	2.860	
2. T axis°	40.00	19.57	32.20	9.990	16.40	3.330	5.480	

*Shipley and Hallaran⁸†Wilson⁵‡Katz and co-workers⁹

The variance ratios provide a satisfactory measure for comparing the consistency of different electrocardiographic items. By their very nature the ratios are abstract numbers. It is useful to supplement them with measures of consistency expressed in the units (time or voltage) in which the items are actually measured. Standard deviations (the square roots of the variances) serve this purpose.

RESULTS

Standard Deviations as Measures of the Variability of Electrocardiographic Items.—The variability of electrocardiographic items, as characterized by the interindividual, intraindividual, and error-of-measurement standard deviations, is indicated in Tables I (limb leads) and II (chest leads). In addition, the range for the various items was calculated on the basis of 90 per cent expectancy. For the purpose of condensation, only the values of P_2 are given as representative for the P wave. Also, the Q waves and S waves in the limb leads were omitted; they were absent or very small in the majority of our subjects.

TABLE II. MEANS, STANDARD DEVIATIONS (INTERINDIVIDUAL, INTRAINDIVIDUAL, AND ERROR OF MEASUREMENT), AND 90 PER CENT RANGE OF ELECTROCARDIOGRAPHIC ITEMS; CHEST LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

AMPLITUDES (MM.)	MEAN	INTERINDIVIDUAL		INTRAINDIVIDUAL		ERROR OF MEASUREMENT	
		S.D.	90% RANGE (\pm)	S.D.	90% RANGE (\pm)	S.D.	90% RANGE (\pm)
1. R-CF ₁	2.14	0.42	0.70	0.27	0.44	.091	.150
2. R-CF ₂	6.14	2.44	4.00	0.58	0.96	.327	.538
3. R-CF ₄	13.01	7.23	11.90	1.60	2.60	.371	.616
4. S-CF ₁	16.68	5.87	9.70	1.31	2.20	.406	.668
5. S-CF ₂	24.88	9.15	15.10	2.27	3.70	.514	.845
6. S-CF ₄	5.57	3.69	6.10	1.30	2.10	.500	.822
7. RS-T-CF ₁	0.20	0.35	0.57	0.19	0.31	.170	.280
8. RS-T-CF ₂	1.17	0.60	0.98	0.44	0.73	.522	.859
9. RS-T-CF ₄	0.71	0.56	0.92	0.35	0.58	.432	.711
10. T-CF ₁	-3.06	1.41	2.30	0.57	0.93	.228	.375
11. T-CF ₂	6.82	1.94	3.20	0.84	1.40	.268	.441
12. T-CF ₄	7.29	2.01	3.30	0.86	1.40	.359	.591
13. R/S-CF ₁	0.15	0.09	0.14	0.02	0.03	.008	.013
14. R/S-CF ₂	0.29	0.18	0.29	0.05	0.09	.017	.028
15. R/S-CF ₄	4.55	5.73	9.40	3.05	5.00	.982	1.620

The variation within individuals is smaller than the variation between individuals, as would be expected for almost any physiologic function; but it is by no means negligible. The variation due to error of measurement obviously plays only a minor role in general. In this section we are primarily

concerned with the day-to-day (intraindividual) variation of repeated electrocardiograms. It may be noted that the daily variability of the R wave in the chest leads is definitely larger than in the limb leads; the 90 per cent range for R in CF₄ (mean, 13.01 mm.) is ± 2.6 mm.; that for R₂ (mean, 12.81 mm.), ± 1.1 millimeters. The daily variability of the quotient R/S is small for CF₁ and CF₂, while it is enormous in CF₄. The variability of the RS-T segment is larger in the chest leads than in the limb leads. Also, the variability of the T wave is quite large; for instance, for T in CF₂ the 90 per cent range of daily variation is from 8.2 to 5.4 millimeters.

In order to make possible a comparison of the intraindividual variation in different electrocardiographic items, the standard deviations or the calculated 90 per cent range may be expressed in some cases as percentages of the mean. Such a procedure is used at times, but it is valid only when the biologic range starts from zero and goes up to a well-defined upper limit. This is not the case for many electrocardiographic characteristics.

A better procedure is to relate the intraindividual variability to the differences between clinically "normal" individuals, expressed as the range of commonly accepted normal limits. These limits are shown in the last column of Table I. No such normal limits are given for the chest leads (Table II) because the norms are less adequate. For illustration, the 90 per cent range of intraindividual variability in percentage of the accepted normal range for the P-R interval is 31.0 per cent; for the QRS interval, 33.0 per cent; for the amplitude of the R wave in Lead II, 11.6 per cent; for the RS-T segment in Lead II, 24.0 per cent; and for the amplitude of the T wave in Lead II, 21.9 per cent.

Statistically, the "normal ranges" are less satisfactory criteria of individual differences than the standard deviations. As these latter are simply the square roots of the variances, in the next section we shall deal directly with them.

Variances and Variance Ratios.—Tables III and IV show the variances (intraindividual variance, V_{wl} ; random variance, V_R ; and interindividual or "within days" variance, V_{wD}) and the derived consistency coefficients for the various items in limb leads (Table III) and chest leads (Table IV). The ratio of V_{wl} and V_R for all electrocardiographic measurements is very close to 1.00. Consequently, it makes practically no difference which of the two variances is used for calculation of the consistency.

It can be seen that the consistency of the R wave in repeated measurements is high compared to that of the T wave. The amplitudes of R and T in Lead II have a higher degree of consistency than in Lead I or III; probably this reflects the effect of axis variability. The consistency of both the QRS and the T axis is poorer than that of the corresponding amplitudes. The poorer consistency of R in CF₁ and of S in CF₄, compared to the R and S waves in the

TABLE III. VARIANCES AND THE DERIVED CONSISTENCY MEASURES EXPRESSED AS PERCENTAGES (100 V_{wI}/V_{wD} , 100 V_R/V_{wD}), AND COEFFICIENTS OF CONSISTENCY ($r'_c = 1 - V_{wI}/V_{wD}$; $r_c = 1 - V_R/V_{wD}$); LIMB LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

	V_{wI}	V_R	V_{wD}	V_{wI}/V_R	$\frac{100 V_{wI}}{V_{wD}}$	$\frac{100 V_R}{V_{wD}}$	r'_c	r_c
Intervals								
1. R-R	73.75	75.85	175.07	0.972	42.1	43.3	.579	.567
2. Δ Max-Min R-R	29.18	30.64	47.56	0.952	61.4	64.4	.386	.356
3. P-R	0.73	0.66	5.45	1.11	13.4	12.1	.866	.879
4. QRS	0.16	0.16	1.72	1.00	9.3	9.3	.907	.907
5. K_{QT}	.00023	.00024	.00045	0.954	51.1	53.3	.486	.461
6. $K_{syst.}$.00013	.00012	.00029	1.03	44.8	41.4	.553	.568
Amplitudes								
1. P_2	0.020	0.021	0.059	0.952	33.9	35.6	.661	.644
2. R_1	0.30	0.30	3.91	1.00	7.7	7.7	.923	.923
3. R_2	0.41	0.38	18.29	1.08	2.2	2.1	.978	.979
4. R_3	0.68	0.64	27.65	1.06	2.5	2.3	.975	.977
5. Σ_{QRS}	2.23	2.13	76.22	1.05	2.9	2.8	.971	.972
6. RS- T_1	0.023	0.024	0.029	0.958	79.3	82.8	.207	.172
7. RS- T_2	0.033	0.033	0.039	1.00	84.6	84.6	.154	.154
8. RS- T_3	0.024	0.023	0.055	1.04	43.6	41.8	.564	.582
9. T_1	0.150	0.153	0.819	0.980	18.3	18.7	.817	.813
10. T_2	0.193	0.189	3.21	1.02	6.0	5.9	.940	.941
11. T_3	0.196	0.192	1.30	1.02	15.1	14.8	.846	.854
12. Σ_T	0.663	0.639	10.70	1.04	6.2	6.0	.938	.940
Axis								
1. QRS axis	43.05	43.11	272.83	.999	15.8	15.8	.842	.842
2. \bar{T} axis	99.79	103.48	382.94	.964	26.1	27.0	.739	.730

TABLE IV. VARIANCES AND THE DERIVED CONSISTENCY CHARACTERISTICS EXPRESSED AS PERCENTAGES ($\frac{100 V_{wI}}{V_{wD}}$; $\frac{100 V_R}{V_{wD}}$) AND COEFFICIENTS OF CONSISTENCY ($r'_c = 1 - \frac{V_{wI}}{V_{wD}}$; $r_c = 1 - \frac{V_R}{V_{wD}}$); CHEST LEADS: ELEVEN REPETITIONS IN TWELVE SUBJECTS

AMPLITUDES	V_{wI}	V_R	V_{wD}	$\frac{V_{wI}}{V_R}$	$\frac{100 V_{wI}}{V_{wD}}$	$\frac{100 V_R}{V_{wD}}$	r'_c	r_c
1. R- CF_1	0.071	0.068	0.178	1.04	39.9	38.2	.601	.618
2. R- CF_2	0.339	0.332	5.97	1.02	5.7	5.6	.943	.945
3. R- CF_4	2.56	2.28	52.25	1.12	4.9	4.4	.951	.956
4. S- CF_1	1.71	1.64	34.44	1.04	5.0	4.8	.950	.952
5. S- CF_2	5.15	5.02	83.80	1.03	6.1	6.0	.939	.940
6. S- CF_4	1.70	1.70	13.61	1.00	12.5	12.5	.875	.875
7. RS-T- CF_1	0.036	0.037	0.122	0.973	29.5	30.3	.705	.697
8. RS-T- CF_2	0.195	0.201	0.356	0.970	54.8	56.5	.452	.435
9. RS-T- CF_4	0.124	0.125	0.310	0.992	40.0	40.3	.600	.597
10. T- CF_1	0.320	0.302	1.99	1.06	16.1	15.2	.839	.849
11. T- CF_2	0.706	0.696	3.76	1.02	18.8	18.5	.811	.814
12. T- CF_4	0.735	0.786	4.02	0.935	18.3	19.6	.816	.803
13. R/S- CF_1	0.000422	0.000429	0.00743	0.984	5.7	5.8	.943	.942
14. R/S- CF_2	0.00278	0.00286	0.0313	0.972	8.9	9.1	.911	.909
15. R/S- CF_4	9.31	9.61	32.88	0.969	28.3	29.2	.717	.708

other two chest leads, may be due to the smaller amplitude and the consequently greater inaccuracy of measurement. For a convenient survey, the various electrocardiographic items are grouped according to the degree of consistency in Table V.

TABLE V. ELECTROCARDIOGRAPHIC ITEMS, GROUPED ACCORDING TO DEGREE OF CONSISTENCY AS CHARACTERIZED BY r'_c

CONSISTENCY	r'_c	ITEMS
Very high	>0.9	QRS int.; R_1 ; R_2 ; R_3 ; Σ_{QRS} ; T_1 ; T_2 ; Σ_T ; R-CF ₂ ; R-CF ₄ ; S-CF ₁ ; S-CF ₂ ; R/S-CF ₁ ; R/S-CF ₂
High	0.89-0.80	P-R int.; QRS axis; S-CF ₄ ; T-CF ₁ ; T-CF ₂ ; T-CF ₄ ; T_3
Moderate	0.79-0.70	T axis; RS-T-CF ₁ ; R/S-CF ₄
Low	0.69-0.60	P_2 ; R-CF ₁ ; RS-T-CF ₄
Very low	<0.60	R-R int.; $\Delta_{max-min}$ R-R; K_{QT} ; $K_{syst.}$; RS-T ₁ ; RS-T ₂ ; RS-T ₃ ; RS-T-CF ₂

As far as we are aware, the only published material on repeated electrocardiographic determinations is that of Lewis.³ Table VI shows the comparison of the Minnesota series and Lewis' series. In general, the consistency values are strikingly similar, but most items show a somewhat better consistency in the Minnesota material. It is possible that better physiologic standardization was a contributing factor.

Correction of the Consistency Measures for Homogeneity of the Sample.—The variance "within days," V_{wD} , is the best available estimate of the magnitude of the differences between individuals in the population from which the given sample of subjects was drawn. When we deal with small samples of subjects, highly homogeneous with respect not only to age and sex but also to over-all physical "fitness," the value V_{wD} will tend to be smaller than for more heterogeneous samples, and the apparent consistency of the electrocardiographic items will be low.

We tested this effect by substituting for V_{wD} a value obtained on a larger sample drawn from the same population as our smaller sample. The latter value was obtained under standard conditions on a group of thirty-six men. In addition, we calculated the day-to-day consistency in our material using the data on the variation between individuals in Wilson's⁵ material of 104 cases and Graybiel and McFarland's¹ material of 1,000 cases.

Table VII shows the intraindividual variances obtained in the present group of twelve subjects (first column), the interindividual variances (standard deviations squared) of the larger samples (second column), and the corrected consistency indices. No such corrections could be made for the chest leads. Comparison of Table VII with Table III shows an appreciable improvement in consistency for the following items: R-R interval, P_2 , RS-T₁, RS-T₂, RS-T₃,

TABLE VI. COMPARISON OF CONSISTENCY CHARACTERISTICS IN LEWIS' AND IN THE PRESENT (MINNESOTA) MATERIAL FOR SELECTED ELECTROCARDIOGRAPHIC ITEMS

ITEMS	SOURCE	NUMBER OF SUBJECTS	NUMBER OF REPETITIONS	V _{wI}	V _n	V _{wD}	$\frac{V_{wI}}{V_n}$	$\frac{100 V_{wI}}{V_{wD}}$	$\frac{100 V_n}{V_{wD}}$	r' _c	r _c
P ₂	Lewis Minn.	16 12	2 11	0.024 0.020	0.025 0.021	0.052 0.059	0.960 0.952	46.2 33.9	48.1 35.6	.538 .661	.519 .644
R ₁	Lewis Minn.	16 12	2 11	0.078 0.30	0.065 0.30	1.89 3.91	1.20 1.00	4.13 7.7	3.44 7.7	.959 .923	.966 .923
R ₂	Lewis Minn.	16 12	2 11	0.461 0.41	0.403 0.38	4.00 18.29	1.14 1.08	11.53 2.2	10.08 2.1	.885 .978	.899 .979
R ₃	Lewis Minn.	16 12	2 11	1.281 0.68	1.365 0.64	9.09 27.65	0.938 1.06	14.1 2.5	15.0 2.3	.859 .975	.850 .977
T ₁	Lewis Minn.	16 12	2 11	0.128 0.150	0.130 0.153	0.535 0.819	0.985 0.980	23.9 18.3	24.3 18.7	.761 .817	.757 .813
T ₂	Lewis Minn.	16 12	2 11	0.301 0.193	0.321 0.189	1.112 3.21	0.938 1.02	27.1 6.0	28.9 5.9	.729 .940	.711 .941
T ₃	Lewis Minn.	16 12	2 11	0.214 0.196	0.228 0.192	0.472 1.30	0.939 1.02	45.3 15.1	48.3 14.8	.547 .846	.517 .854
R-R	Lewis Minn.	16 12	2 11	99.81 73.75	105.60 75.85	273.03 175.07	0.945 0.972	36.6 42.1	38.7 43.3	.634 .579	.613 .567
P-R	Lewis Minn.	16 12	2 11	0.375 0.73	0.400 0.66	2.30 5.45	0.938 1.11	16.3 13.4	17.4 12.1	.837 .866	.826 .879

QRS axis, and T axis. Most of these items are in the low or poor consistency group (Table V). Most of the items with high consistency were not improved.

TABLE VII. THE CONSISTENCY CHARACTERISTICS OBTAINED BY USING THE BEST AVAILABLE ESTIMATE OF THE VARIATION OF A GIVEN ELECTROCARDIOGRAPHIC VARIABLE IN THE NORMAL POPULATION

	V_{wI}	SD^2	$\frac{100 V_{wI}}{SD^2}$	CORR. r'_c
Intervals				
1. R-R	73.75	246.18*	29.96	.700
2. Δ Max-Min R-R	29.18	49.00†	59.55	.404
3. P-R	0.73	(4.84)*	(15.08)	(.849)
4. QRS	0.16	(1.00)*	(16.00)	(.840)
5. K_{QT}	0.00023	(.00031)†	(74.2)	(.258)
6. $K_{syst.}$	0.00013	(.00025)†	(52.0)	(.480)
Amplitudes				
1. P_2	0.020	0.152*	13.16	.868
2. R_1	0.30	6.6*	4.55	.955
3. R_2	0.41	(15.1)*	2.72	.973
4. R_3	0.68	(17.6)*	3.86	.961
5. Σ_{QRS}	2.23	(60.06)†	(3.71)	(.963)
6. RS- T_1	0.023	0.0399*	57.6	.424
7. RS- T_2	0.033	0.104*	31.7	.683
8. RS- T_3	0.024	0.096*	25.0	.750
9. T_1	0.150	(0.781)*	(19.21)	(.808)
10. T_2	0.193	(1.4)*	(13.79)	(.862)
11. T_3	0.196			
12. ΣT	0.663	(6.30)†	(10.52)	(.895)
Axis				
1. QRS Axis	43.05	542.89*	7.93	.921
2. T Axis	99.79	552.72†	18.05	.819

Parentheses were placed around values for those electrocardiographic characteristics for which $SD^2 < V_{wD}$.

* = Graybiel and associates.¹

† = Control values in the Minnesota Starvation Experiment.

Correction of the Consistency Measures for the Error of Measurement.—Three independent measurements were made on one electrocardiogram from each of the twelve subjects. The data yielded a two-way table, similar in structure to the data obtained by actually making separate electrocardiographic determinations on different days. This body of data was analyzed by the techniques of the analysis of variance. Tables VIII and IX show the corrected intraindividual variances obtained by using the values of V_{wM} , the variance "within measurements," for correction, and the corrected consistency indices. The last column of Tables VIII and IX shows the proportion of the error of measurement, V_{wM} , in terms of the percentage of uncorrected V_{wI} .

The error of the measurement itself is the major source of the total day-to-day variation (>50 per cent of V_{wI}) in the following items: P-R and QRS interval, RS-T segments in Leads I, CF_2 , and CF_4 ; it is an appreciable source of variation (20 to 50 per cent of V_{wI}) for K_{Q-T} , RS- T_2 , RS- T_3 , and R in CF_2 .

TABLE VIII. VARIANCE OF THE DERIVED CONSISTENCY CHARACTERISTICS OBTAINED BY CORRECTING THE INTRAINDIVIDUAL VARIANCE FOR ERRORS OF MEASUREMENT (V_{WM}): CORR. $V_{WI} = (V_{WI} - V_{WM})$: LIMB LEADS

	V_{WM}	V_{WI}	V_{WD}	$\text{CORR. } V_{WI} = (V_{WI} - V_{WM})$	$\frac{100 \text{ CORR. } V_{WI}}{V_{WD}}$	CORRECTED r'_c	$\frac{100 V_{WM}}{V_{WI}}$
Intervals							
1. R-R	.083	73.75	175.07	73.67	42.1	.579	0.11
2. $\Delta\text{Max-Min R-R}$.542	29.18	47.56	28.64	60.2	.398	1.86
3. P-R	.375	0.73	5.45	0.36	6.61	.934	51.3
4. QRS	.125	0.16	1.72	0.035	2.03	.980	78.1
5. $\bar{K}Q_T$.000054	0.00023	0.00045	0.000176	39.11	.609	23.5
6. $K_{\text{syat.}}$.000024	0.00013	0.00029	0.000105	36.55	.634	18.5
Amplitudes							
1. P_2	.0025	0.020	0.059	0.018	30.5	.695	12.5
2. R_1	.0096	0.30	3.91	0.29	7.4	.926	3.2
3. R_2	.017	0.41	18.29	0.39	2.1	.979	4.1
4. R_3	.050	0.68	27.65	0.63	2.3	.977	7.4
5. Σ_{QRS}	.108	2.23	76.22	2.12	2.8	.972	4.8
6. $RS-T_1$.012	0.023	0.029	0.011	37.9	.621	52.2
7. $RS-T_2$.007	0.033	0.039	0.026	66.7	.333	21.2
8. $RS-T_3$.010	0.024	0.055	0.014	25.5	.745	41.7
9. T_1	.0079	0.150	0.819	0.142	17.3	.827	5.3
10. T_2	.012	0.193	3.21	0.181	5.6	.944	6.2
11. T_3	.013	0.196	1.30	0.183	14.1	.859	6.6
12. Σ_T	.025	0.663	10.70	0.638	6.0	.940	3.8
Axis							
1. QRS Axis	3.04	43.05	272.83	40.01	14.7	.853	7.1
2. T Axis	11.08	99.79	382.94	88.71	23.2	.768	11.1

TABLE IX. VARIANCE OF THE DERIVED CONSISTENCY CHARACTERISTICS OBTAINED BY CORRECTING THE INTRINDIVIDUAL VARIANCE FOR ERRORS OF MEASUREMENT: $\text{CORR. } V_{wI} = (V_{wI} - V_{wM})$; CHEST LEADS

ITEMS	V_{wM}	V_{wI}	V_{wD}	$\text{CORR. } V_{wI}$	$\frac{100 \text{ CORR. } V_{wI}}{V_{wD}}$	r'_e	$\frac{100 V_{wM}}{V_{wI}}$
1. R-CF ₁	.0083	0.071	0.178	0.063	35.4	.646	11.7
2. R-CF ₂	.107	0.339	5.97	0.232	3.9	.961	31.6
3. R-CF ₄	.138	2.56	52.25	2.42	4.6	.954	5.4
4. S-CF ₁	.165	1.71	34.44	1.55	4.5	.955	9.6
5. S-CF ₂	.264	5.15	83.80	4.89	5.8	.942	5.1
6. S-CF ₄	.250	1.70	13.61	1.45	10.7	.893	14.7
7. RS-T-CF ₁	.029	0.036	0.122	0.007	5.7	.943	80.6
8. RS-T-CF ₂	.273	0.195	0.356				
9. RS-T-CF ₄	.187	0.124	0.310				
10. T-CF ₁	.052	0.320	1.99	0.268	13.47	.865	16.3
11. T-CF ₂	.072	0.706	3.76	0.634	16.86	.831	10.2
12. T-CF ₄	.129	0.735	4.02	0.606	15.07	.849	17.6
13. R/S-CF ₁	.000063	0.000422	0.00743	0.000359	4.83	.952	14.9
14. R/S-CF ₂	.000296	0.00278	0.0313	0.00248	7.92	.921	10.6
15. R/S-CF ₄	.964	9.31	32.88	8.35	25.4	.746	10.3

The improvement of consistency obtained by eliminating the error of measurements can be seen by comparison of Tables III and VIII, or IV and IX. After the correction, the poor-consistency items ($r'_c < 0.6$) are reduced from eight to four.

DISCUSSION

From the point of view of repeatability, there are no absolute criteria for judging whether a given electrocardiographic item is or is not satisfactory. The grading of consistency from very high to very low in Table V is essentially arbitrary, a matter of judgment and agreement. The meaning of the measures of consistency may be clarified by considering the term $\%V_{wi}$, defined in Formula 4 as the ratio of the intraindividual ("within individuals") to the interindividual ("within days") variance. When the value $\%V_{wi}$ approaches zero, the particular electrocardiographic item is highly characteristic of the individual. When the intraindividual variance approaches 100 per cent of the interindividual variance, the electrocardiographic item is not a stable individual characteristic. A low consistency may be due either to large day-to-day fluctuations in the particular function (and, in part, to the inaccuracies of the measurements) or to the compression of the range of the individual differences, that is, an extreme homogeneity of the sample. The present sample of twelve subjects may appear small. However, there is evidence that the interindividual variability in the greater part of the electrocardiographic items was actually not much different from the variability in much larger samples, including Graybiel and McFarland's material (1,000 subjects).

For clinical electrocardiography, the determination of the intraindividual standard deviations and the 90 per cent range limits are probably the most important results of the present study. Variations within this range are entirely within the limits of variability to be expected by "chance," that is, resulting from a complex of uncontrolled factors, and should not be interpreted as improvement or deterioration in patients. It seems safe to assume that the intra-individual variability of patients will not be smaller than that of normal subjects. The agreement as to the variability of repeated determinations in the present material and in that of Lewis is surprisingly good, in spite of the fact that the samples were obtained on different continents and the determinations were separated by an interval of thirty-six years. This gives assurance that these data may be used for evaluating the significance of changes produced by stress or therapy.

The variability was studied over a comparatively short period of two months; consequently, the data cannot be used for the prediction of variations during considerably longer intervals. It should be pointed out that the repeated determinations were in the basal state. Under less rigorously standardized conditions, the intraindividual variability would increase. For example, it has been shown that such factors of everyday life as eating a meal of moderate size may change significantly the electrocardiogram of patients as well as of normal individuals.^{6,7} Also, in subjects differing from those used in the present study in age, physical

activity, emotional status, and so forth, the range of day-to-day variations may be different. Further information on this point is needed.

Proper consideration of intraindividual variability is especially important for the interpretation of electrocardiograms on the borderline of clinical normality. If the mean of repeated determinations of an electrocardiographic item is outside the limits of clinical normality, the electrocardiogram should be interpreted as abnormal, even when the values fall occasionally within the normal limits. Conversely, if the mean falls within the normal limits, the occasional values beyond these limits should not be regarded as indicators of abnormality. It is evident that for a more precise interpretation of borderline cases serial electrocardiograms are necessary.

SUMMARY

Electrocardiograms were taken on twelve normal young men in the basal state on eleven different occasions over a period of two months. Three standard and three chest leads were used, and thirty-five electrocardiographic items were measured. In addition, one set of electrocardiograms was measured by the same assistant on three different occasions.

The amount of variation contributed by interindividual differences, by day-to-day physiologic fluctuation, and by inaccuracy in measuring the records was determined statistically.

The ratio of the intraindividual to the interindividual variance was used as the criterion of the consistency of repeated electrocardiographic determinations. Out of thirty-five electrocardiographic items, the consistency was very high (consistency coefficient ≥ 0.90) in fourteen, high (0.89 to 0.80) in seven, moderate (0.79 to 0.70) in three, low (0.69 to 0.60) in three, and very low (< 0.60) in eight.

The consistency measures were corrected for the homogeneity of the sample of subjects by substituting estimates of interindividual variance based on much larger samples, and for the inaccuracy of measurement of the electrocardiographic records.

The 90 per cent expectancy range of intraindividual variability was calculated. These data may be applied for interpretation of borderline electrocardiograms and for evaluation of degrees of deterioration or improvement in serial electrocardiograms.

We wish to express our thanks and appreciation to Miss A. Bjella, Mr. A. Butler, Mr. W. Steinberger, and Mr. W. Thompson for their assistance in this study.

REFERENCES

1. Graybiel, A., McFarland, R., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, *AM. HEART J.* **27**:524-1944.
2. Viscidi, P. C., and Geiger, A. J.: Electrocardiographic Observations on 500 Unselected Young Adults at Work, *AM. HEART J.* **26**:763, 1943.
3. (a) Lewis, T., and Gilder, M. D.: The Human Electrocardiogram: A Preliminary Investigation of Young Male Adults, to Form a Basis for Pathological Study, *Phil. Tr. Roy. Soc. B.* **202**:351, 1912.
(b) Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, New York, 1921, Paul B. Hoeber, Inc.
4. Brozek, J., and Alexander, H.: A Note on Estimation of the Components of Variation in a Two-Way Table, *Am. J. Psychol.* **60**:629, 1947.
5. Wilson, F. N.: Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, *Tr. A. Life Insur. M. Dir. America* **24**:96, 1937.
6. Simonson, E., Alexander, H., Henschel, A., and Keys, A.: The Effect of Meals on the Electrocardiogram in Normal Subjects, *AM. HEART J.* **32**:202, 1946.
7. Simonson, E., McKinlay, C. A., and Henschel, A.: Effect of Meals on the Electrocardiogram of Cardiac Patients, *Proc. Soc. Exper. Biol. & Med.* **63**:542, 1946.
8. Shipley, R. A., and Hallaran, W. R.: The Four-Lead Electrocardiogram in 200 Normal Men and Women, *AM. HEART J.* **11**:325, 1936.
9. Katz, L. N., Goldman, A. M., Langendorf, R., Kaplan, L. G., and Killian, S. T.: The Diagnostic Value of the Electrocardiogram Based on an Analysis of 143 Autopsy Cases, *AM. HEART J.* **24**:627, 1942.

A STUDY OF THE Q-T INTERVAL IN RHEUMATIC FEVER

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RECENT studies by Ashman¹ and by Taran and Szilagyi² have indicated that during the course of acute rheumatic fever the Q-T interval may become prolonged and constitute an important sign of rheumatic activity. Because of this, we decided to reinvestigate this subject. We studied the electrocardiograms of 100 young patients in Lincoln Hospital up to the age of 20 years. Of these, fifty patients had active rheumatic fever, twenty-five patients were in the quiescent stage, and, as a control group, twenty-five additional cases were studied by us. All patients had sinus rhythm. The only medication the patients received was salicylates, unless otherwise noted.

METHOD

Electrocardiographic studies were done on all 100 patients. Lead II was used for the measurement of the Q-T interval. Ten successive cycles were measured and the average obtained. Serial electrocardiograms were taken on all the active cases, and, in addition, the patients' clinical courses were followed, with frequent blood counts, erythrocyte sedimentation rates, and temperature (rectal) and pulse studies.

We used the following method of analyzing variations in the Q-T interval. Since the Q-T interval varies with the ventricular rate, more or less complicated formulas must be used. One of the simplest is that devised by Bazett, namely, $Q-T = k \sqrt{R-R}$, where k is a constant and $R-R$ is the interval between two successive R waves.³ Bazett pointed out that k is the same in men and children, but longer in women, and described the constant as 0.37 for men and children and 0.40 for women. We used the constant 0.40 for all of our cases. This value corresponds to that used by Taran and Szilagyi.

Thus, in order to calculate accurately whether a measured Q-T interval is prolonged, it must be compared with the ideal Q-T interval determined from Bazett's formula. The relation between the measured Q-T interval and the ideal Q-T interval can then be described as a percentage or a ratio. For example, let us suppose there is a tracing in which the heart rate is 75, the Q-T interval is 0.40 second, and the R-R interval is 0.80 second. From Bazett's formula, the ideal Q-T interval is 0.358 second. The measured Q-T interval is, however,

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Read at the Scientific Session of the New York Heart Association, March 23, 1948.

TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER

ELECTROCARDIOGRAPHIC DATA										CLINICAL DATA			
CASE	AGE	SEX	ECG DATE*	RATE	Q-T	R-R	Q-Tr†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)		
1	8	F	4/14/44	83	0.34	0.76	0.98	98.2	56	17,900	Initial temperature of 104°, with gradual decline to normal; polyarthrits; polyarthrits one year before		
			4/27/44	67	0.36	0.90	0.95	99.4	34	—			
			5/17/44	61.5	0.38	0.98	0.96	99.0	34	—			
			6/20/44	85	0.34	0.70	1.02	100.0	28	6,200			
			7/17/44	77	0.34	0.78	0.96	98.2	20	—			
2	11		10/ 8/46	110	0.34	0.54	1.16	100.0	95	13,150	Temperature never exceeded 101°; polyarthrits, chest pain, dyspnea; ECG showed elevated RS-T segments in all leads, and there was clinical evidence of pericarditis		
			10/11/46	92	0.36	0.64	1.13	99.0	—	—			
			10/29/46	61.5	0.42	0.98	1.07	99.2	45	7,100			
3	8	M	7/ 3/46	93	0.36	0.64	1.13	99.6	76	18,600	Temperature never exceeded 100°; sore throat, arthralgia, anorexia; had polyarthrits one year before		
			7/10/46	93	0.34	0.64	1.07	100.0	—	—			
			7/22/46	100	0.36	0.60	1.16	99.6	19	10,400			
4	15	M	5/21/46	110	0.30	0.54	1.03	100.6	85	8,400	Temperature never exceeded 100.6°; polyarthrits and erythema multiforme; had polyarthrits at age of 10		
			5/31/46	87	0.32	0.68	0.97	98.6	95	—			
			6/24/46	115	0.30	0.52	1.04	98.6	75	—			
5	19	M	5/10/46	70	0.40	0.90	1.06	100.2	40	—	Temperature never exceeded 101°; polyarthrits		
			5/14/46	68.6	0.40	0.88	1.07	98.6	—	6,100			
			5/17/46	68.6	0.40	0.88	1.07	98.6	—	—			
6	15	F	5/ 7/46	70.5	0.34	0.84	0.93	102.6	120	12,000	Initial temperature of 103.4°, with gradual decline to normal; polyarthrits		
			5/15/46	70.5	0.36	0.84	0.98	99.0	120	—			
			5/27/46	75	0.36	0.80	1.01	98.6	75	7,000			
7	11	F	7/10/46	135	0.26	0.44	0.98	99.8	78	13,400	Temperature never exceeded 100.2°; polyarthrits and dyspnea; went on to develop congestive heart failure and was digitalized shortly before death		
			7/22/46	130	0.30	0.46	1.11	99.6	38	—			
			7/30/46	130	0.28	0.46	1.04	98.6	36	—			
			8/ 2/46*	125	0.32	0.48	1.16	99.0	—	—			
7	11	M	5/21/46	105	0.32	0.56	1.07	100.0	80	13,150	Temperature never exceeded 100.4°; polyarthrits		
			5/27/46	115	0.32	0.52	1.11	99.4	59	—			
			6/12/46	83	0.36	0.72	1.07	99.0	22	6,100			

8	13	F	1/ 2/45 1/18/45	70.5 81	0.36 0.34	0.84 0.74	0.98 0.99	99.4 99.8	117 68	17,450 —	Initial temperature of 104°, with gradual decline to normal; polyarthritis; abdominal pains
9	2½	NI	12/19/42 12/22/42 12/24/42 1/ 4/43 1/11/43 1/25/43 2/ 8/43 3/ 8/43	135 150 120 120 115 115 105 115	0.24 0.26 0.24 0.22 0.24 0.28 0.28 0.26	0.44 0.40 0.50 0.50 0.52 0.52 0.56 0.52	0.91 1.03 0.85 0.78 0.83 0.98 0.94 0.90	100.2 100.0 100.4 100.2 100.0 99.0 99.4 99.0	120 — — 90 — — 60 8	16,000 — — 10,000 — 10,800 13,000 10,000	Temperature never exceeded 100.6°; abdominal pains, chills, anorexia; developed clinical and roentgenologic evidence of pericarditis and pericardial effusion
10	4½	F	12/ 5/44 12/18/44 1/20/45	125 115 93	0.28 0.28 0.32	0.48 0.52 0.64	1.01 0.97 1.00	102.0 99.8 99.0	110 50 4	21,200 — 6,050	Initial temperature of 103.2°, with gradual decline to normal; arthralgia, sore throat
11	8	NI	11/ 1/45 11/21/45 12/ 6/45	125 91 68.6	0.28 0.32 0.36	0.48 0.66 0.88	1.01 0.98 0.96	103.0 99.0 99.8	50 23 41	10,200 — 12,300	Initial temperature of 104°, with gradual decline to normal; polyarthritis
12	11	NI	5/22/44 5/29/44 6/ 9/44 6/27/44 7/ 3/44	125 77 72 87 93	0.26 0.36 0.36 0.34 0.34	0.48 0.76 0.72 0.68 0.66	0.94 1.04 1.07 1.04 1.05	103.8 99.0 99.0 99.0 99.0	44 99 49 11 —	18,000 — — 9,200 —	Initial temperature of 104.2°, with gradual decline to normal; polyarthritis
13	12½		4/28/45	69	0.38	0.90	1.01	99.0	55	14,450	Initial temperature of 101°, with gradual decline to normal; anorexia, vague abdominal pains
	14½	M	3/11/46 3/19/46	83 96	0.34 0.32	0.72 0.62	1.01 1.02	99.2 99.0	52 12	8,900 —	Initial temperature of 102°, with gradual decline to normal; polyarthritis
	14½		4/ 5/46	70.5	0.36	0.84	0.98	98.6	45	—	Initial temperature of 101°, with rapid decline to normal; admitted because of fever at home
14	9½	F	3/30/44 4/10/44 4/27/44	100 70.5 93	0.32 0.38 0.34	0.60 0.84 0.64	1.04 1.04 1.07	99.2 99.0 99.0	125 13 14	21,750 14,200 12,000	Temperature never exceeded 99.4°; polyarthritis
	12		2/15/47 3/10/47	105 110	0.32 0.28	0.56 0.54	1.07 0.95	102.8 102.2	97 63	16,900 —	Initial temperature of 103.2°, with gradual decline to normal; polyarthritis; large pulmonary cones on x-ray of chest

TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER—(CONTINUED)

CASE	AGE	SEX	ELECTROCARDIOGRAPHIC DATA						CLINICAL DATA			
			ECG DATE*	RATE	Q-T	R-R	Q-Tr†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)	
	12		3/28/47	105	0.36	0.56	1.21	99.0	60	9,700	Normal temperature throughout course; polyarthritides	
15	12	M	8/ 1/46 8/12/46	77 55	0.38 0.36	0.78 0.88	1.08 0.97	101.0 98.6	120 97	6,800 —	Initial temperature of 101°, with gradual decline to normal; polyarthralgia, polyuria, anorexia, malaise	
	12½		11/26/46	87	0.36	0.68	1.09	98.6	42	—	Normal temperature throughout course; chorea	
16	5	F	2/18/47 3/ 6/47 3/18/47 3/22/47*	125 115 142 115	0.28 0.28 0.28 0.28	0.48 0.52 0.42 0.52	1.02 0.97 1.08 0.97	100.0 99.0 100.2 99.4	124 104 88 —	19,500 — — —	Temperature never exceeded 100.6°; polyarthritides, precordial pain; went on to develop congestive heart failure and was digitalized shortly before death	
17	4	M	2/21/47 3/12/47	103 125	0.32 0.32	0.58 0.48	1.05 1.16	102.0 100.0	108 61	22,000 —	Initial temperature of 103°, with gradual decline to normal; polyarthritides and abdominal pain	
18	16	M	2/24/47	79	0.30	0.76	0.86	101.0	90	17,700	Initial temperature of 101°, with rapid decline to normal; polyarthritides	
19	8	F	7/15/41 8/ 8/41 8/19/41	105 93 100	0.30 0.32 0.32	0.56 0.64 0.60	1.01 1.00 1.03	99.2 100.0 99.0	25 18 19	12,000 9,200 —	Temperature never exceeded 100.4°; arthralgia	
20	5	M	1/29/47 2/18/47	125 100	0.28 0.34	0.48 0.60	1.02 1.11	99.4 98.2	95 11	10,500 —	Initial temperature of 101°, with gradual decline to normal; arthralgia, anorexia	
21	13	M	7/ 7/46 8/15/46	87 83	0.40 0.36	0.68 0.72	1.21 1.07	101.0 99.8	103 60	14,000 8,650	Initial temperature of 103.4°, with gradual decline to normal; polyarthritides	
22	20	F	4/25/46 5/ 2/46 5/16/46 5/27/46 5/29/46 6/24/46	115 105 110 93 96 93	0.32 0.34 0.34 0.34 0.36 0.34	0.52 0.56 0.54 0.64 0.62 0.64	1.11 1.14 1.14 1.07 1.15 1.07	99.8 99.0 98.6 100.0 99.0 99.0	135 122 51 45 28 30	9,900 — — — — —	Temperature never exceeded 100°; precordial sticking pain, arthralgia, dyspnea, and anorexia; polyarthritides three years earlier; treated for syphilis at the age of 19	

23	13	F	6/18/46 7/ 3/46	70.5 48	0.44 0.40	0.84 1.18	1.20 0.93	100.0 99.0	118 85	12,000 —	Temperature never exceeded 100.5°; polyarthritis
24	7	F	7/19/46 7/31/46	110 90	0.30 0.32	0.54 0.66	1.03 0.98	100.2 99.8	140 25	13,700 —	Initial temperature of 102.6°, with gradual decline to normal; polyarthritis, epistaxis, chills
25	5	M	6/26/46 7/ 2/46	93 105	0.32 0.30	0.62 0.56	1.01 1.01	99.0 99.6	118 110	12,950 —	Initial temperature of 101°, with gradual decline to normal; polyarthritis, pharyngitis
26	7	F	2/15/45 2/19/45 3/ 8/45	115 105 90	0.30 0.32 0.36	0.52 0.56 0.66	1.04 1.07 1.11	99.8 99.0 99.0	115 — 25	22,500 — —	Initial temperature of 101°, with gradual decline to normal; abdominal pain; developed clinical and roentgenologic evidence of pericardial and right pleural effusion
27	8		2/ 5/46 2/14/46	85 75	0.36 0.38	0.70 0.80	1.08 1.07	99.0 99.2	92 55	7,400 —	Normal temperature throughout course; chest pain, dyspnea and orthopnea
27	11	F	3/24/45 5/24/45	135 90	0.28 0.34	0.66 0.66	1.06 1.05	102.0 99.0	123 25	14,050 6,800	Initial temperature of 102°, with gradual decline to normal; polyarthritis
27	13		11/15/46 11/22/46	90 90	0.32 0.32	0.68 0.72	0.98 0.98	99.0 99.0	52 30	14,150 —	Normal temperature throughout course; dyspnea and hemoptysis; E.H., M.I., and M.S.
28	9	M	4/26/40 5/ 9/40	93 63	0.36 0.36	0.64 0.96	1.13 0.92	102.0 99.2	95 8	8,800 7,700	Initial temperature of 103.2°, with gradual decline to normal; recurrent polyarthritis for three years; E.H., M.I., M.S., and A.I.
28	16		7/10/47 7/22/47	97 57	0.30 0.40	0.62 1.04	0.95 0.98	100.0 98.6	56 10	7,400 —	Temperature never exceeded 100°; polyarthritis, E.H., M.I., M.S., A.I., and A.S.; P-R interval: 0.32 and 0.20, respectively
29	6½	M	5/ 5/47 5/23/47	100 83	0.32 0.32	0.46 0.72	1.16 0.94	100.0 99.2	63 18	10,000 —	Initial temperature of 102°, with gradual decline to normal; polyarthritis at 4 and 5 years; headache and polyarthritis
30	10	M	3/25/47 4/ 2/47	125 125	0.32 0.32	0.48 0.48	1.16 1.16	100.0 99.4	33 37	8,200 7,400	Initial temperature of 102.2°, with gradual decline to normal; RHD at 8 years; polyarthritis
31	4	F	1/ 8/47 1/13/47 2/18/47	150 150 97	0.24 0.28 0.32	0.40 0.40 0.60	0.95 1.11 1.04	102.2 100.0 99.2	120 — 58	24,000 — 15,300	Initial temperature of 102.2°, with gradual decline to normal; anorexia, abdominal pain, nausea, vomiting, and convulsions; had clinical evidence of pericarditis

TABLE I. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN FIFTY CASES OF ACTIVE RHEUMATIC FEVER—(CONTINUED)

CASE	AGE	SEX	ECG DATE	ELECTROCARDIOGRAPHIC DATA						CLINICAL DATA			
				RATE	Q-T	R-R	Q-Tr†	TEMP.‡	E.S.R.	W.B.C.	REMARKS§ (° F. throughout)		
32	9	F	5/21/47	103	0.28	0.58	0.93	99.0	48	12,200	Temperature never exceeded 100.8°; polyarthritis, erythema nodosum		
33	11	M	2/18/47	100	0.28	0.60	0.90	100.0	91	7,600	Initial temperature of 101°, with gradual decline to normal; polyarthritis		
34	17	M	5/ 1/47	81	0.34	0.74	0.99	101.0	93	9,600	Initial temperature of 103°, with gradual decline to normal; polyarthritis		
35	16	M	1/ 9/47	79	0.36	0.76	1.04	99.0	95	19,600	Initial temperature of 102.6°, with gradual decline to normal; polyarthritis and dyspnea		
36	14	M	3/27/47	103	0.32	0.58	1.05	99.0	30	10,300	Initial temperature of 102.4°, with gradual decline to normal; polyarthritis, anorexia		
37	3	F	3/ 8/45	135	0.26	0.44	0.98	99.8	130	—	Temperature never exceeded 99.8°; polyarthritis		
	5		2/11/47	100	0.32	0.60	1.03	99.2	125	19,950	Temperature normal throughout course; polyarthritis		
38	4½	F	5/20/43	110	0.28	0.54	0.95	99.2	12	9,400	Temperature never exceeded 100°; epistaxis and polyarthritis		
	5		12/ 8/43	120	0.28	0.50	0.99	100.0	48	6,600	Temperature never exceeded 100°; epistaxis, restlessness		
	8		4/ 2/47	103	0.32	0.58	1.06	99.2	73	14,300	Initial temperature of 101°, with gradual decline to normal; epistaxis and polyarthritis		
39	4	F	3/ 3/39	125	0.28	0.48	1.01	103.2	94	21,800	Initial temperature of 103.2°, with gradual decline to normal; polyarthritis and dyspnea		
40	13	M	1/ 9/47	83	0.42	0.72	1.24	98.6	98	—	Normal temperature throughout course; polyarthritis		

41	11	M	9/13/46	83	0.38	0.72	1.13	99.0	49	4,900	Initial temperature of 101°, with gradual decline to normal; polyarthritides; RHD at 9 years of age
	12		4/22/47	93	0.36	0.64	1.13	99.2	40	11,300	Temperature never exceeded 100°; tachycardia, nausea, precordial pain
42	14	F	4/17/47	83	0.36	0.72	1.07	99.0	28	14,600	Temperature never exceeded 100.4°; polyarthritides
43	11	M	5/14/43 6 26 43	87 60	0.34 0.38	0.68 1.00	1.04 0.95	101.0 99.8	35 8	10,000	Initial temperature of 102°, with gradual decline to normal; polyarthritides, nausea, and vomiting
44	11	F	4/18/47	105	0.30	0.56	1.01	99.2	106	10,900	Temperature never exceeded 100°; polyarthritides
45	10	M	5/19/47	81	0.32	0.66	0.98	100.4	88	12,800	Initial temperature of 101°, with gradual decline to normal; polyarthritides
46	5	F	6/23/47	125	0.26	0.44	0.98	100.0	44	8,600	Temperature never exceeded 100°; polyarthritides
47	14	M	1/18/46	93	0.28	0.64	0.87	101.0	90	18,300	Initial temperature of 102°, with gradual decline to normal; long history of colds and epistaxis; polyarthritides
	15		5/ 6/47	103	0.32	0.58	1.05	101.0	94	11,250	Initial temperature of 101.6°, with gradual decline to normal; polyarthritides; M.I., M.S.
48	7	F	5/16/46	77	0.38	0.78	1.16	99.0	125	15,000	Initial temperature of 102°, with gradual decline to normal; polyarthritides, nausea
49	14	F	3/30/46 4/12/46	100 77	0.32 0.36	0.60 0.78	1.03 1.02	99.0 99.0	52 50	8,100	Temperature never exceeded 100°; polyarthritides
50	13	F	5/27/47 7/22/47 8/ 8/47	115 71 71	0.30 0.32 0.36	0.52 0.84 0.84	1.03 0.87 0.98	100.2 100.0 99.0	120 52 10	12,300	Initial temperature of 100.4°, with gradual decline to normal; epistaxis and cough; M.I. and M.S. on admission, which gradually disappeared

*Taken just before death and after digitalization.

†Q-T ratio (the ratio of actual to ideal Q-T interval).

‡Maximum temperature on day electrocardiogram was taken. See also Remarks.

§E.H., enlarged heart. R.H.D., rheumatic heart disease. M.I., mitral insufficiency. M.S., mitral stenosis. A.S., aortic stenosis. A.I., aortic insufficiency.

0.40 second; this is $\frac{0.400}{0.358}$ greater than normal. Calculating this as a percent-

age, one obtains the value of 112 per cent. Thus, the measured Q-T interval is 112 per cent of the ideal Q-T interval expected for a ventricular rate of 75. A simpler way of expressing this is to say that the *Q-T ratio*, or *Q-T_R*, is 1.12. All calculations of the Q-T ratio were made using a nomogram devised by one of us (E. G.⁴).

RESULTS

General Remarks.—Theoretically, a Q-T ratio above 1.0 is abnormal; however, normal controls frequently give values above this. As a basis for our studies, we calculated Q-T ratios from twenty-five normal children and also maximum values of the Q-T ratio from the data compiled by Ashman and Hull.⁵ We found that the average normal Q-T ratio is 1.01 in men and children. The maximum normal limit of the Q-T ratio for men and children is 1.08.

The Q-T Interval During Active Rheumatic Fever.—Measurements of the Q-T intervals of our fifty active cases are given in Table I, with clinical and laboratory data.

Our results can be summarized as follows:

1. Only fourteen (28 per cent) of our fifty active cases had Q-T ratios longer than the normal maximum value of 1.08.
2. However, twenty-one (42 per cent) other patients had, at one time or another, a Q-T ratio longer than the average normal value of 1.01.
3. Fifteen patients (30 per cent) with active rheumatic fever never showed a Q-T ratio that even reached the normal average values. In many of these cases, it is true, only one electrocardiogram was taken. But we even observed this when serial electrocardiograms were taken (Cases 5, 8, 10, 11, 13, 16, 27, and second admission of 28).

In a general way, the abnormal Q-T ratio went hand in hand with the clinical state of the patient. For example, in Case 6 the Q-T interval became markedly prolonged just before death. However, marked discrepancies occurred. For example, in Case 9 the Q-T interval remained within normal limits even during an attack of acute pancarditis and pericarditis. Case 1 had normal Q-T intervals during her first admission for polyarthritis, but prolongation of the Q-T interval occurred during her second admission three years later.

No correlation could be made between the Q-T intervals and laboratory data such as erythrocyte sedimentation rate and white blood count.

The Q-T Interval in Quiescent Cases of Rheumatic Fever.—One of the advantages believed to be obtained by measuring the Q-T interval is that this interval should be normal in cases of quiescent rheumatic fever. Study of our twenty-five quiescent cases (Table II) bears this out. None of the patients had a longer Q-T ratio than the maximum normal value of 1.08. However, eight of our patients had Q-T ratios longer than the average Q-T ratio of 1.01. This is in contrast to our twenty-five normal control cases (Table III), where only three had Q-T ratios above 1.01.

TABLE II. ELECTROCARDIOGRAPHIC AND CLINICAL DATA IN TWENTY-FIVE CASES OF QUIESCENT RHEUMATIC FEVER

CASE	AGE	SEX	RATE	Q-T	R-R	Q-Tr*	REMARKS†
1	6	F	100	0.28	0.60	0.99	Acute rheumatic episode six months before
2	6	F	105	0.28	0.56	0.94	Acute rheumatic episode one year before
3	7	M	81	0.32	0.74	0.93	History of an attack of RHD
4	13	F	73	0.32	0.82	0.88	History of an attack of RHD
5	17	M	79	0.34	0.76	0.98	History of an attack of RHD, E.H., and M.I.
6	14	M	79	0.34	0.76	0.98	History of an attack of RHD
7	15	F	110	0.30	0.54	1.03	History of an attack of RHD, M.I., and M.S.
8	10	F	105	0.30	0.56	1.01	History of an attack of RHD
9	15	F	73	0.36	0.82	0.99	History of an attack of RHD
10	15	M	63	0.36	0.96	0.93	Multiple rheumatic episodes: E.H., M.I., M.S., A.I., and A.S.
11	14	M	69	0.34	0.88	0.91	Acute rheumatic episode three years before
12	20	M	65	0.33	0.92	0.86	History of an attack of RHD, E.H., and M.I.
13	14	F	87	0.32	0.68	0.97	Acute rheumatic episode eight years before
14	11	F	100	0.32	0.60	1.03	Chorea two years before
	12		93	0.32	0.64	1.00	Large pulmonary conus and right heart on fluoroscopy
15	11	F	79	0.36	0.76	1.04	Acute rheumatic episode five years before
16	17	F	86	0.32	0.74	0.93	History of dyspnea one year before; M.I. and M.S.
17	15	M	105	0.28	0.56	0.94	History of attacks of RHD; M.I. and M.S.
18	17	F	81	0.34	0.74	0.99	Acute rheumatic episode at the age of 11
19	9	M	100	0.30	0.60	0.97	Acute rheumatic episode one year before
20	9	M	93	0.28	0.64	0.87	Acute rheumatic episode two years before
21	7	F	79	0.32	0.76	0.92	Acute rheumatic episode four months before
22	10	F	85	0.34	0.70	1.02	Acute rheumatic episode three years before
23	13	F	71	0.34	0.84	0.94	Acute rheumatic episode four years before
24	10	F	87	0.32	0.68	0.97	Acute rheumatic episode five months before
25	2½	M	120	0.28	0.50	0.99	Acute rheumatic episode with pericarditis three months before

*Q-T Ratio (the ratio of actual to ideal Q-T interval).

†RHD, rheumatic heart disease; E.H., enlarged heart; M.I., mitral insufficiency; M.S., mitral stenosis; A.I., aortic insufficiency; A.S., aortic stenosis.

TABLE III. ELECTROCARDIOGRAPHIC DATA IN TWENTY-FIVE NORMAL CHILDREN AND YOUNG ADULTS

CASE	AGE	SEX	RATE	Q-T	R-R	Q-Tr*
1	7	F	115	0.28	0.52	0.97
2	16	M	75	0.36	0.80	1.01
3	18	F	83	0.32	0.72	1.00
4	15	F	60	0.41	1.00	1.03
5	14	M	69	0.34	0.88	0.91
6	12	F	87	0.32	0.68	0.97
7	7	M	100	0.28	0.60	0.91
8	20	F	64	0.42	0.98	1.07
9	8	F	87	0.32	0.68	0.97
10	20	M	79	0.34	0.76	0.98
11	14	M	67	0.34	0.90	0.89
12	14	M	63	0.40	0.96	1.03
13	14	F	100	0.30	0.60	0.97
14	9	F	90	0.32	0.66	0.98
15	10	M	87	0.32	0.64	1.00
16	9	F	87	0.28	0.64	0.87
17	15	F	83	0.34	0.72	1.01
18	9	M	83	0.34	0.72	1.01
19	11	F	79	0.32	0.76	0.92
20	5	F	115	0.24	0.52	0.83
21	9	M	97	0.30	0.62	0.97
22	10	F	65	0.32	0.92	0.83
23	4	F	87	0.30	0.68	0.91
24	6	M	110	0.28	0.54	0.95
25	7	F	93	0.31	0.64	0.97

*Q-T Ratio (the ratio of actual to ideal Q-T interval).

DISCUSSION

Our results are somewhat in conflict with those recently reported by Taran and Szilagyi,² who found an abnormal Q-T interval in all their cases of active rheumatic fever. They, however, used a different index, namely "a corrected Q-T interval or Q-T_c." The Q-T_c, however, is also based on Bazett's formula, $Q-T = k \sqrt{R-R}$. The maximum normal Q-T_c which they found was 0.405.

Our results can be compared with theirs because a Q-T_c of 0.405 roughly corresponds to a Q-T ratio of 1.01. Thus, even according to their criteria, 30 per cent of our active cases had normal Q-T_c values. Part of the discrepancy between their results and ours may be due to the type of cases studied. None of their patients was over 14 years of age, whereas we included patients up to 20 years of age. The exact cause of the prolongation of the Q-T interval that occurs in rheumatic fever is unknown.

CONCLUSIONS

In our study of the Q-T interval in rheumatic fever, as measured by the Q-T ratio, we found that marked prolongation of the Q-T ratio beyond a maximum normal value of 1.08 occurred in only 28 per cent of our cases of active rheumatic fever. However, in 42 per cent more of the active cases, the Q-T ratio was longer than the average normal value of 1.01. Thus, a total of 70 per cent of our active cases had a Q-T ratio longer than average. This is in contrast to the fact that only 12 per cent of our normal control subjects had Q-T ratios above average.

In our quiescent cases of rheumatic fever there were no abnormal Q-T ratios, but 24 per cent had Q-T ratios above average.

Thus, we may conclude the following:

1. During active rheumatic fever, prolongation of the Q-T interval is not invariable but may occur.
2. During the quiescent state, the Q-T interval is within normal.
3. An abnormal Q-T interval in a patient with a history of previous rheumatic fever is a suggestive sign of rheumatic activity.

We wish to thank Dr. Harry Altman, Director of the Pediatric Service at Lincoln Hospital, for his cooperation.

REFERENCES

1. Ashman, R.: The Normal Duration of the Q-T Interval, *AM. HEART J.* 23:522, 1942.
2. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, *AM. HEART J.* 33:14, 1947.
3. Bazett, H. C.: An Analysis of the Time Relation of Electrocardiograms, *Heart* 7:353, 1918-1920.
4. Goldberger, E.: A Simple Method of Determining Abnormalities of the Q-T Interval, *AM. HEART J.* 36:141, 1948.
5. Ashman, R., and Hull, E.: Cited by Burch, G., and Winsor, T.: A Primer of Electrocardiography, Philadelphia 1945, Lea & Febiger, p. 193.

Clinical Reports

RECOVERY FROM SUBACUTE BACTERIAL ENDOCARDITIS (STREPTOCOCCUS FECALIS)

REPORT OF TWO CASES

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THE literature is replete with reports of patients who have been cured of subacute bacterial endocarditis since the advent of penicillin. The vast majority of these patients were, however, infected with *Streptococcus viridans*. The treatment of patients infected with *Streptococcus fecalis* has remained generally unsatisfactory. Isolated reports of cures have been published. Mac Neal¹ cured a patient with subacute bacterial endocarditis who was infected with *S. fecalis* by using Thiobismol, neoarsphenamine, bacteriophage, and penicillin. Hunter² treated five patients infected with *S. fecalis*, some with streptomycin alone, and some with streptomycin and penicillin. Four of the five patients were not helped, but one patient was cured. Organisms of the patient cured were sensitive to 3.5 micrograms of streptomycin per cubic centimeter, and therapy consisted of a total of 125 Gm. of streptomycin given over a period of thirty-two days and 4 million units of penicillin given daily for four weeks. This patient was reported to be well ten months after therapy was completed.

Indications are that more of these patients can be cured if sufficient amounts of penicillin are given. We have treated two patients with the disease, both of whom were infected with extremely resistant strains of *S. fecalis*.

The organisms isolated from our patients were identified as *S. fecalis* by Dr. Marcus A. Krupp, head of our clinical laboratory. The organisms were gram-positive cocci which grew in short chains, were not bile-soluble, and grew in 6.5 per cent solution of sodium chloride, as well as in 0.1 per cent methylene blue.

CASE REPORTS

CASE 1.—C. G., a 53-year-old white man, was admitted to the Veterans' Administration Hospital at San Francisco on July 26, 1946, for continuance of penicillin therapy for subacute bacterial endocarditis. He had probably been ill for one year previous to his admission, because at that time he noticed that he began to tire quite easily and began to run a low-grade

From the Veterans' Administration Hospital, San Francisco, Calif.

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fever, which was present for a few hours each day. During the next several months he went to a physician, who gave him sulfonamide drugs, and to a chiropractor, who prescribed a low-fat diet and manipulation of the spine. At the end of five to six months of this treatment he felt worse, had lost about fifty pounds in weight, and was beginning to develop dyspnea and ankle edema. On May 8, 1946, his physician sent him to a local hospital, where a diagnosis of sub-acute bacterial endocarditis was established. *S. fecalis* was identified in his blood culture. He was started on 20,000 units of penicillin every three hours, and his dosage was gradually increased, so that at the end of five weeks he was receiving 800,000 units every three hours. His blood cultures, however, remained positive for *S. fecalis*. He continued to run a low-grade fever and developed petechiae over the arms and legs. On June 21, 1946, he was transferred to the Stanford University Hospital, where sensitivity tests revealed that a concentration of 10 units of penicillin per cubic centimeter of media were required to inhibit his organisms, and it was further determined that 1.5 million units of penicillin every three hours, or 12 million units of penicillin per day, were required to maintain an adequate blood level. His blood penicillin level reached 100 units per cubic centimeter, and this level was probably reached because of the renal lesion the patient had at this time. A blood culture taken after one week of this therapy was sterile. Simultaneously his symptoms began to disappear.

He was transferred to this hospital on July 26, 1946. At that time he was still well nourished and did not appear acutely ill. Abnormal physical findings were limited to the heart and abdomen. The pulse rate was 80 per minute and regular. His heart was not enlarged. A harsh systolic murmur was heard, loudest over the apex, but also heard over the left sternal border. No diastolic murmurs or thrills were present. The blood pressure was 140/80. The spleen was enlarged to one and one-half inches below the left costal margin and the liver was enlarged a similar distance below the right costal margin. No petechiae were seen.

The total red blood cell count was 4 million, with 11 Gm. of hemoglobin. The white blood cell count was 7,400, with a normal differential. Urinalysis showed a small amount of albumin. There were 17 white blood cells per high dry field and 4 red blood cells per high dry field of a centrifuged specimen. An occasional granular cast was seen. A twenty-four hour Addis count showed 360,000 granular casts, 18 million white blood cells, and 164.4 million red blood cells. The total protein excreted in a twenty-four hour urine specimen was 1.6 grams. The blood urea nitrogen was 33.2 mg. per 100 c.c. and the blood creatinine was 2.8 mg. per 100 cubic centimeters. Blood Wassermann and Kahn tests were negative. Electrocardiograms were normal, and x-ray films of the chest confirmed that the heart was not enlarged. The treatment was continued, and the patient received 1.5 million units of amorphous penicillin every three hours, because crystalline penicillin was not available to us at that time. Because of the great pain suffered with these injections, after three days the patient refused to continue with this therapy and stated that he would rather die than take any more injections. Fortunately, we were able to obtain crystalline penicillin at this time, and the treatment was continued on a similar dosage of the crystalline preparation, without further difficulty. This therapy was continued until August 22, at which time the patient had completed sixty days of effective therapy and had received a total of 720 million units of penicillin. At this time penicillin therapy was stopped, and all laboratory tests were essentially normal except for a slight elevation of the sedimentation rate, which remained about 20 mm. per hour, and a trace of albumin in the urine. After the start of his intensive penicillin therapy the patient had no positive blood cultures. He was discharged from the hospital on Nov. 15, 1946, and has been seen every month since that time. His urine continued to show a trace of albumin for about six months after his discharge from the hospital, and then became clear. His blood cultures have been consistently sterile, and at this time the blood count, urinalysis, sedimentation rate, electrocardiogram, and chest x-ray film are well within normal limits. The apical systolic heart murmur is still present, but the spleen and liver can no longer be felt. He has no evidence of infection or cardiac failure. He has worked daily at his regular job as a salesman and has no complaints whatsoever at this time, eighteen months after his discharge from the hospital.

CASE 2.—E. D., a 49-year-old white man, was admitted to the hospital on Jan. 8, 1947, complaining of a painful swollen area on his left temple. In 1933, fourteen years previous to his admission to this hospital, he had an episode of acute urinary retention because of a urethral stricture, the result of an acute gonococcal urethritis which he developed in 1917. In October, 1946, he had a recurrence of acute urinary retention and was admitted to a Naval Hospital. He was told that he had a urethral stricture, and sounds were passed. It was at this time that he developed a round, swollen area on the lateral aspect of the left ankle, which was quite tender, and a low-grade fever. Therapy consisted of hot packs to the ankle and oral sulfadiazine. After ten days of treatment the swelling, pain, and fever completely subsided and he was discharged from the hospital and remained well for two months.

Then four days previous to the patient's admission to this hospital (three months later) he developed a swollen, tender area over the left temple and ran a fever between 101° and 102° F. for the two evenings preceding his admission. He had no other complaints whatsoever. At the time of entry he was well nourished and well developed. He had a fever of 99.6° Fahrenheit. There was a 4.0 by 5.0 cm. raised area on the left temple overlying the left temporal artery, an area which was quite painful to pressure. This lesion was not fluctuant. It was noted that the left temporal artery could be felt pulsating proximal to the lesion, and although the artery could be felt distal to the lesion, no pulsation could be discerned there. The patient's lungs and heart were entirely normal. The pulse rate was 78 per minute and regular. The blood pressure was 114/88. Neither the liver nor the spleen could be felt. The left peroneal artery was occluded. This lesion probably developed in October, 1946. There was a marked similarity between the lesions of the left temporal artery and the left peroneal artery. Pulsation of the branch of the left peroneal artery was present proximal but not distal to the site of the lesion described in the previous hospital entry. Otherwise the physical examination was not remarkable.

His urine showed a faint trace of albumin and 10 to 12 white blood cells per high dry field in a centrifuged specimen. No casts or red blood cells were present. The sedimentation rate was 24 mm. in one hour. The red blood cell count was 4,370,000, with 12 Gm. of hemoglobin. The white blood cell count was 10,000, with 45 per cent segmented cells, 13 per cent nonsegmented cells, 34 per cent lymphocytes, 6 per cent monocytes, and 2 per cent eosinophils. Blood Wassermann and Kahn tests were negative. The electrocardiogram and the chest films were not remarkable.

The patient continued to have a low-grade fever. On Jan. 18, 1947, a biopsy was taken of the left temporal artery at the site of the lesion, as well as of the left peroneal artery at the site of the previous lesion. These sections revealed a diffuse panarteritis of both vessels. No thrombi or organisms were seen. After three weeks of hospitalization the patient's spleen was first felt just below the left costal margin. Repeated examinations of the patient revealed no cardiac disease. Blood cultures, however, showed a heavy growth of *S. fecalis*. On January 21, the organisms were found to be insensitive to a concentration of 20 units of amorphous penicillin per cubic centimeter, but were sensitive to 1.0 unit of streptomycin per cubic centimeter. On February 3, the patient was started on 0.5 Gm. of streptomycin given intramuscularly every three hours. On February 8, the organisms had increased their resistance to a point where they were no longer inhibited by 25 units of streptomycin per cubic centimeter. Streptomycin therapy was therefore stopped, and the patient was started on 0.5 Gm. of sulfadiazine and 0.5 Gm. of sulfathiazole every three hours orally. Retest of the organisms on February 24 showed that they were sensitive to between 1.5 and 2.0 units of crystalline penicillin G per cubic centimeter. Retest of the original organisms showed them also to be sensitive to between 1.5 and 2.0 units of crystalline penicillin G in contrast to the apparently high resistance the organisms showed when tested with amorphous penicillin. On March 20, the patient was started on 2.5 million units of crystalline penicillin every three hours, or 20 million units per day. Between the time of admission and the beginning of this therapy the patient had thirteen successive blood cultures which showed *S. fecalis*. On March 13, the patient suddenly developed pain and redness at the tip of the left fifth finger. The lesion disappeared in a few days. Blood cultures made on March 24 and March 28, about ten weeks after the patient's admission to the hospital, were sterile, but the patient did not

remain afebrile until the first of April. On April 4, three months after admission to this hospital and fifteen days after the start of penicillin therapy, a loud aortic diastolic murmur was heard for the first time, although the patient had been examined daily by members of the house staff and consultants' staff. Blood pressure at that time was 100/60. On April 15, a Grade 2 apical systolic murmur appeared. The laboratory tests remained essentially unchanged except for an eosinophilia, which at times reached 20 per cent. The patient continued to receive penicillin and blood transfusions until May 18, at which time penicillin was stopped. He had received 20 million units of penicillin a day for sixty days, or a total dosage of 1.2 billion units of penicillin.

The patient was discharged from the hospital on May 29, 1947, and was asymptomatic. He has come back to our follow-up clinic every month since his discharge, and has been working daily as an automobile mechanic. His blood count and sedimentation rate have remained normal and his blood cultures have remained sterile. His electrocardiogram reveals no changes. The aortic diastolic murmur persists, as does the apical systolic murmur.

DISCUSSION

The treatment of subacute bacterial endocarditis requires the administration of adequate amounts of a suitable antibiotic to inhibit growth of the causative organisms. It is of the utmost importance, therefore, that the sensitivity of the organisms to the antibiotic be tested in all cases of subacute bacterial endocarditis. We have used penicillin as our antibiotic of choice. The testing of the sensitivity of the organisms has been stressed by Bloomfield¹ and others, but its particular importance when *Streptococcus fecalis* is being dealt with has not been emphasized. When patients with *S. fecalis* infection receive adequate dosages of penicillin, their disease is apparently no harder to cure than the disease of those patients who are infected with the more sensitive *S. viridans*. We have no reason to believe that their sequelae should be different or more severe. We used no agents to blockade the renal excretion of penicillin, although it is conceivable that some patients may require this measure. One of our patients had a renal lesion which in itself contributed to maintaining an extremely high penicillin blood level. Because of the resistance of *S. fecalis*, artificial measures for the blockade of renal excretion of penicillin might otherwise have been required for him.

Because of the pain induced by the administration of amorphous penicillin in the amounts required for these patients, it is imperative to use crystalline penicillin if the intramuscular route, which we consider the most satisfactory, is to be used.

SUMMARY

Two patients suffering from subacute bacterial endocarditis caused by *S. fecalis* have been presented. Because of the insensitivity of this organism to antibiotics now available, massive doses were used. One of these patients received 12 million units of penicillin a day for sixty days, or a total dosage of 720 million units of crystalline penicillin. The other patient received 20 million units a day, or a total dosage of 1.2 billion units. Both of these men are asymptomatic at this time and have shown no clinical or laboratory evidences of recurrence of their disease since their discharge from the hospital.

The organisms of one of the patients were at first quite sensitive to streptomycin, being inhibited by 1 unit of the drug per cubic centimeter of medium. After the patient had received 4.0 Gm. of streptomycin intramuscularly for forty-eight hours, however, the organisms were resistant to 25 units of streptomycin per cubic centimeter of medium. It thus became impossible to reach effective therapy by the use of streptomycin for this patient.

It is of importance to note that this same patient's organisms were insensitive to 20 units of amorphous penicillin per cubic centimeter but were sensitive to between 1.5 and 2.0 units of crystalline penicillin. Whether this was due to deterioration of the amorphous penicillin or whether a substandard drug was used is not known. In view of the above findings, however, we believe that crystalline penicillin should be used not only because of its more constant potency but also because of the fact that it is less painful to administer.

It is interesting to note that the one patient developed his initial arteritis six months before he showed any clinical evidence of cardiac involvement. In spite of careful daily search, the valvular lesion did not become evident until the fifteenth day after penicillin therapy had been started.

REFERENCES

1. Bloomfield, A. L.: Relationship of Strain Sensitivity to Penicillin Dosage in Subacute Bacterial Endocarditis. Address given before the 18th Annual Post-Graduate Symposium of the Heart Disease Committee of the San Francisco Tuberculosis Association, Oct. 30, 1947.
2. Hunter, T. H.: Use of Streptomycin in the Treatment of Bacterial Endocarditis, *Am. J. Med.* 2:436, 1947.
3. MacNeal, W. J., Blevins, A., and Poindexter, C. A.: Clinical Arrest in Enterococcal Endocarditis, *Am. J. M. Sc.* 211:40, 1946.

DELAYED DEATH FOLLOWING CONTUSION OF THE HEART

REPORT OF A CASE

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THE symptoms and consequences of nonpenetrating traumatic injuries to the heart have not always been recognized and have been the subject of much dispute in the recent past. Interest in these lesions was reawakened in this country when Beck,^{1,2} Bright,¹ Moritz,^{3,4} and Atkins³ published the results of their observations on such injuries and of experiments conducted to reproduce them. They explored their mode of origin, symptoms, the anatomic and histologic changes produced by them, and possible methods of treatment.

In their historical review of the literature from 1850 on, Beck and Bright¹ collected twelve cases in which the patients had survived the trauma and thirteen in which they had died of myocardial failure. Stern,⁵ in his exhaustive chapters on traumatic diseases of the heart, amplified this list and added other cases from his own experience. The studies made by these authors formed an important step in the acceptance of the diagnosis of contusion of the heart as a complex of clinical symptoms and disturbances following the traumatic impact. However, all the authors cited emphasized the necessity of amplifying the literature by additional reports of cases thoroughly examined and, if possible, observed from the time of trauma through post-mortem examination. It is for this purpose that the following case history and observations are presented.

CASE REPORT

A 20-year-old Negro man was struck by an automobile and knocked to the street by the impact. He was conveyed to the hospital, where an x-ray film of the thorax did not reveal any fracture of the bony parts. Therefore, after the administration of first aid for bruised ribs, he was released. The following day he consulted his family physician because of pains in the left side of his chest. He was treated for bruises. Only slight abrasions of the skin were noted. The patient did not remain in bed, but since he felt rather weak and tired, he did not return to work.

Eight days after the injury the patient still did not feel well. A physician found a slightly elevated temperature (under 100° F.) and an accelerated pulse rate. He was treated for a cold and advised to remain in bed for a few days. He seemed to improve after a few days of rest, but two weeks after the accident he complained suddenly of a severe pain in the left side of his chest. He was observed to be alert, but weak and perspiring. His pulse rate was markedly accelerated; his temperature less than 99° Fahrenheit. Because of the rapid collapse, he was sent to a hospital immediately. He was pronounced dead on arrival at the hospital, and was taken to the Cuyahoga County Morgue, where the author performed the post-mortem examination.

From the Office of the Coroner, Cuyahoga County, Ohio.

The history which has been cited is a compilation of the information elicited from the police, the physician who rendered first aid, the family physician, and the doctor who ordered the patient to go to the hospital.

Excerpts From the Autopsy Findings.—There is a linear, whitish, depigmented scar of the skin over the fifth and sixth ribs on the left side, in the parasternal line. This scar measures 3.0 cm. in length and 6.0 to 7.0 mm. in width. Vestiges of hemorrhages are seen in the perichondrium of the cartilages of the sixth to tenth left ribs close to their insertion at the sternum. Cartilages of the sixth, seventh, and eighth ribs on the left side show slightly depressed fractures close to their insertion at the sternal border.



Fig. 1.—Anterior aspect of heart showing area of contusion of wall of left ventricle.

There are about 50 c.c. of yellowish fluid in the pleural sac. The heart is of medium size and weighs 250 grams; the right ventricle measures 8.0 cm. in length and the left ventricle, 10 cm. in length. There are a number of subepicardial ecchymoses crossing and surrounding a grayish, pale area of about 2.0 cm. in diameter at the anterior side of the left ventricle, near its tip. A subepicardial hemorrhage 8.0 mm. in diameter is seen at the lateral side of the left ventricle approximately 3.0 cm. below its base. Several small ecchymoses can be seen at the posterior side of the left ventricle (Fig. 1). The anterior wall of the left ventricle in this area bulges slightly, and its thickness is reduced to about 5.0 mm., of which, on cross section, 2.0 to 3.0 mm. show a brownish discoloration such as is seen after a previous hemorrhage, as described by Moritz and Atkins.³

Further findings reveal patent and elastic coronary arteries and aorta, pulmonary edema, venous congestion of spleen and liver, and cerebral edema.

This case was brought to the attention of Dr. Claude S. Beck, and acknowledgement is hereby made of appreciation and indebtedness to Dr. Beck and Mr. Wolfe for their assistance in the completion of this study. At Dr. Beck's direction, Mr. Wolfe injected both coronary arteries with a barium mass prior to the opening of the heart. X-ray films made before and also after dissection showed a striking decrease in both the number and size of the capillaries in the area at the anterior side of the left ventricle (Fig. 2).

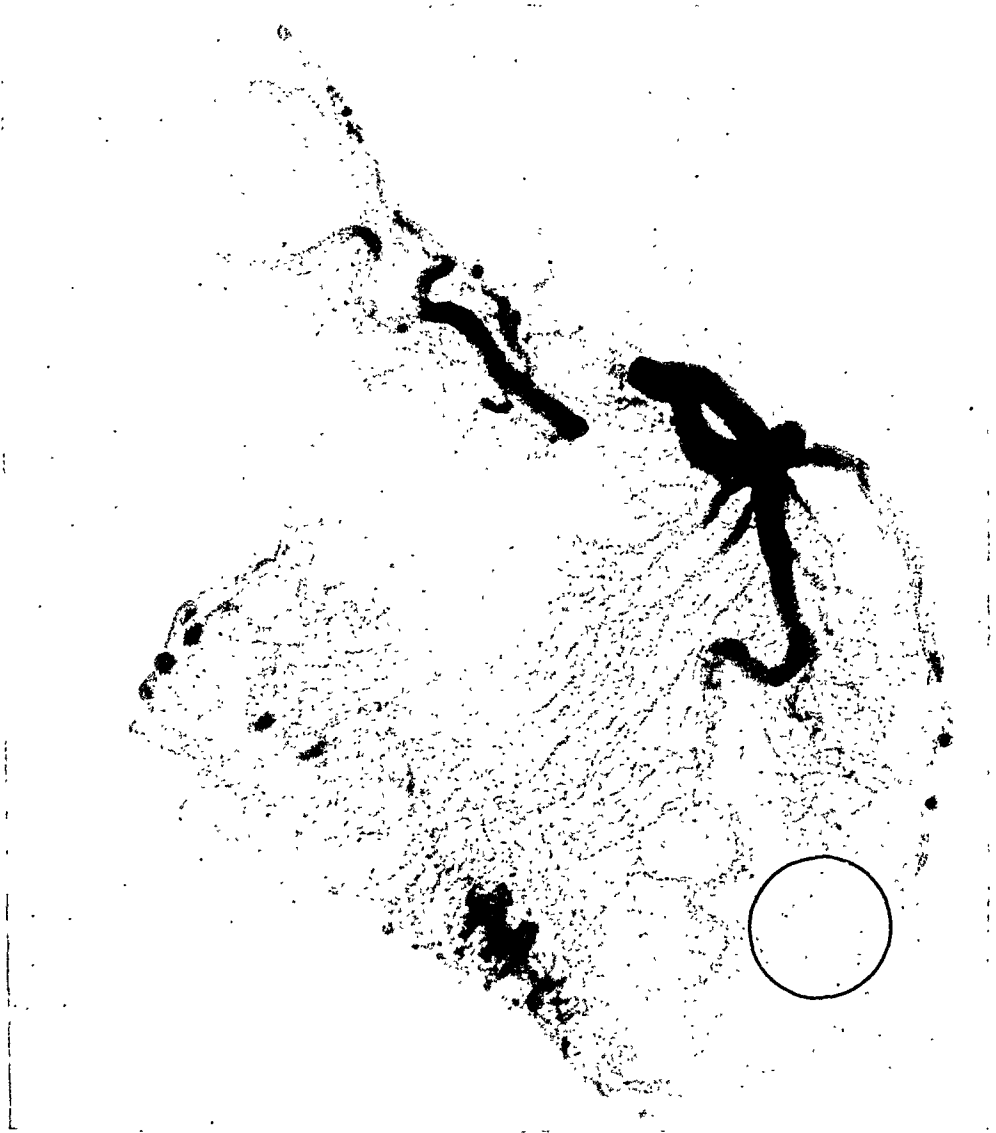


Fig. 2.—X-ray film of the heart showing the decrease in number and size of capillaries at the site of the contusion near the apex of the left ventricle. Coronary arteries were injected with a barium paste.

The microscopic examinations of the grayish, pale area were less impressive. They revealed a somewhat thickened epicardium infiltrated with white cells. The capillaries in the subepicardial layers and the adjoining musculature were more or less collapsed. The patent ones were surrounded by a plasma-like material and by white cells. The loosened interstitial tissue between

the muscle fibers likewise was filled with plasmalike material and white cells, most of which were mononuclear. There was marked fragmentation of muscle fibers (Fig. 3). The microscopic picture from areas of the heart not affected was not abnormal.

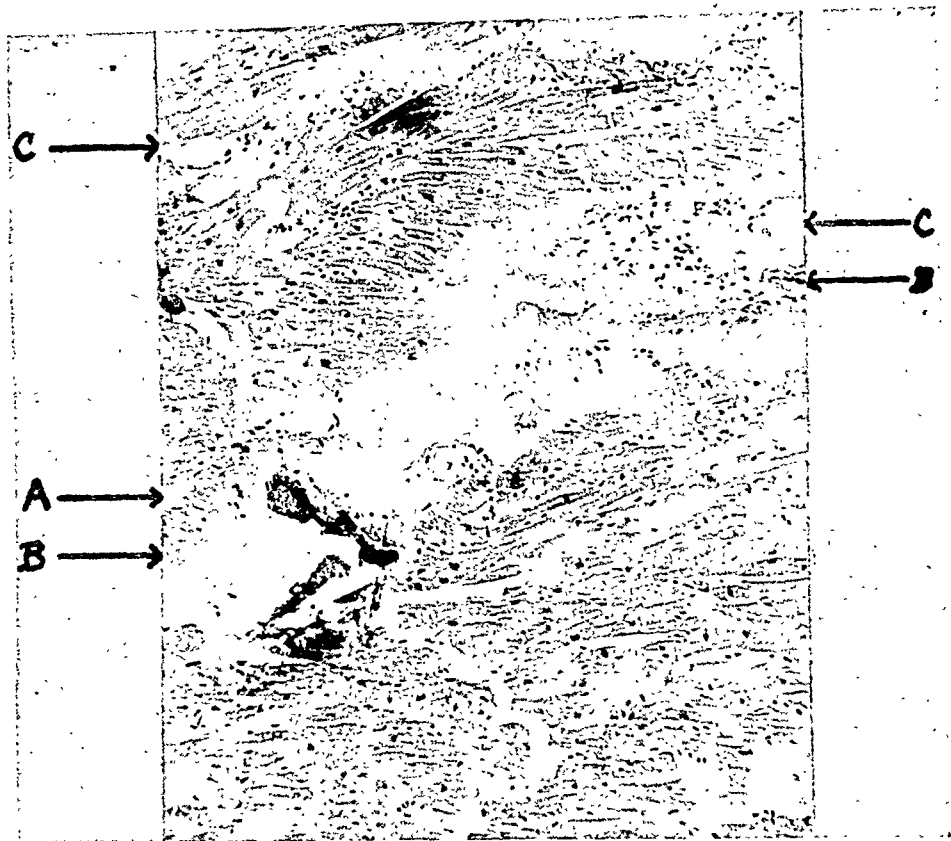


Fig. 3.—Microscopic section of area of contusion. A, injected capillary; B, collapsed capillaries; C, round cells in the interstitial plasmalike material. In various areas throughout the picture fragmentation of the muscle fibers is visible.

DISCUSSION

The gross picture of this heart and the microscopic findings in the area of contusion bear a striking resemblance to the descriptions given by Beck and Bright¹ and Moritz and Atkins.^{3,4} The case history is similar to a case described by Beck.² The fact that death occurred in the second week seems to bear on Beck's² conclusion: "If the patient survives the first nine hours after the accident, his chances of living through the first week are somewhat better than his chances of going through the second week. After the second week it would seem that the area of contusion becomes stronger through the development of scar tissue."

The present case was complicated by the presence of the fractured costal cartilages, which may have caused further aggravation. Unfortunately, there

were no electrocardiograms taken to confirm Beck's assertion that death may occur as a result of ventricular fibrillation in such cases of contusion of the heart.

It is estimated that between 93 and 95 per cent of all cases of contusion of the heart which are not followed by immediate death due to rupture or injuries to other vital organs (as in steering wheel injuries) may heal without further manifest symptoms or noticeable consequences, and may escape clinical recognition.^{6,7}

If, following the advice of Beck¹ and Stern,⁵ every injury to the chest with or without manifest fractures were treated with the possibility of heart contusion in mind, many lives might be saved. The treatment should include bed rest. Repeated electrocardiograms should be taken.

SUMMARY

Contusions of the heart probably occur more frequently than is commonly supposed, and may easily be overlooked. This is indicated by the foregoing report of a case in which a post-mortem examination was made of a 20-year-old man with a history of an accident which at the time was not considered to be serious.

Symptoms displayed several days later were believed to be due to a common cold. Only a few hours before death the patient developed terrific precordial pain and died enroute to the hospital. Autopsy revealed fractures of cartilages of the left costal arch and typical signs of contusion of the heart.

The treatment and origin of contusions of the heart are mentioned.

REFERENCES

1. Beck, C. S., and Bright, E. F.: Nonpenetrating Wounds of the Heart, *AM. HEART J.* **10**:293, 1935.
2. Beck, C. S.: Contusion of the Heart, *J. A. M. A.* **104**:109, 1935.
3. Moritz, A. R., and Atkins, J. P.: Cardiac Contusion, *Arch. Path.* **25**:445, 1938.
4. Moritz, A. R.: *Pathology of Trauma*, Philadelphia, 1942, Lea & Febiger, pp. 143-146.
5. Stern, R. A.: *Trauma in Internal Diseases*, New York, 1945, Grune & Stratton, Inc., pp. 47-156.
6. Arenberg, H.: Traumatic Heart Disease, *Ann. Int. Med.* **19**:326, 1943.
7. Hedinger, C.: Contusio Cordis, *Cardiologia* **12**:46, 1947.

Abstracts and Reviews

Selected Abstracts

Edwards, E. A.: *Nail Changes in Functional and Organic Arterial Disease*. New England J. Med. 239:362 (Sept.), 1948.

The author presents the results of a study of the nails in vasospastic and organic vascular disorders. In such conditions as the cold, stiff, splinted extremity, Raynaud's disease, and scleroderma, the proximal nail fold (the part of the nail plate overlain by skin) becomes very thin and merges gradually into the translucent cuticle. The latter membrane does not end abruptly at its distal or free edge, as it does normally, and is greatly widened. This condition has been termed "pterygium." The changes appear to be an accurate herald of coming scleroderma. They are not seen in the presence of purely organic vascular disorders but appear to be limited to those conditions in which there are vasospastic reflexes mediated through the sympathetic nervous system. Sympathectomy promptly does away with the lesion. In three or four weeks after the operation, the nail fold has become full and the new cuticle is seen growing in its normal sharply delineated manner.

Severe ischemia, due to organic arterial vascular disease, gives rise to a distortion of the growth of the nail plate (nail proper). The linear growth is retarded to the extent that the nail may not have to be trimmed for months or years. The nail plate may increase in thickness, becoming heavy and rough as a result of transverse or eccentrically placed parallel ridging. The nail plate is darkened. The distortion of nail growth may take the form of a claw nail (onychoposis).

An increase of blood supply is signalled by a return of the roughened nail to normal growth, with a rapid distal displacement of the old misshapen nail by a new, more normal portion. The contrast between the old diseased nail and the newer portion serves as a striking indication of the improvement of the circulation and is clinically useful in evaluating the benefit of therapy.

ABRAMSON.

Friedfeld, L., Marcus, H. R., and Vorzimer, J. J.: *Aminophyllin Determination of Circulation Time*. New York State J. Med. 48:2047 (Sept. 15), 1948.

Substances for measuring the circulation time, which produce an end point measurable by objective means, frequently have limited use because of undesirable side reactions. It seemed logical, therefore, to utilize the well-known effect of aminophyllin, which causes a suddenly deepened and rapid respiration, for the determination of the circulation time between the antecubital vein and the respiratory center.

In a series of cases it was found that accurate and definitive results were obtained with but simple preliminary preparation. The patient was placed in a supine position and 1.0 c.c. of a solution containing 0.25 Gm. of aminophyllin was injected as rapidly as possible into the antecubital vein. Timing was done with a stop watch and was calculated from the beginning of the injection to the first appearance of respiratory stimulation. Tabulation of the circulation times obtained in this series revealed a close approximation to the results obtained by the other methods that utilized either test materials with subjective end point or objective measurements with various photoelectric cells, ultraviolet light, or radioactive counters. The time in the majority (80.2 per cent) of these normal cases varied from 12 to 19 seconds, with an average time of 14.6 seconds. This method has special applicability in those cases where the ability of the patient to cooperate in the determination of a subjective end point may be limited by age, language difficulties, cerebral changes, or state of consciousness.

from right to left did not seem very likely. On the whole, the recording of an initial upright, rather than a downward, deflection in Leads V_4 , V_5 , and V_6 was best explained by the supposition that the lesion was too early for complete obliteration of the response to the activating impulse.

CASE 78.—A 60-year-old man gave a four-month history of repeated attacks of typical anginal pain. These attacks came at rest, as well as on exertion, and generally lasted from five to thirty minutes until Jan. 21, 1947, when a prolonged attack of exceptionally severe pain occurred which necessitated hospitalization. Physical examination revealed syphilitic aortic insufficiency and severe congestive heart failure, necessitating maintenance on digitalis throughout hospitalization. On the morning of January 29 he was found in shock with a rapid, totally irregular ventricular rhythm. Quinidine was instituted and continued in a dose of 0.25 Gm. every four hours for the remainder of his hospital stay. A pericardial friction rub was heard for the first time on January 30. Death occurred on Feb. 2, 1947.

Electrocardiographic Findings.—Electrocardiograms selected from a series obtained during his thirteen days of hospital stay are reproduced in Fig. 9. On January 24 sinus rhythm was present. On January 30 there was an auricular tachycardia with auricular rate of 230, usually with variable ventricular response, but with intermittent 2:1 ratio, as seen in Lead V_2 . On February 1 there was a wandering pacemaker between sinus and A-V nodes, well brought out in Lead II. The disturbance in auricular rhythm which developed on January 29 raised the question of extension of an infarct into the atria. The pattern of the QRS complex in the standard leads was fairly typical of left bundle branch block and was quite constant throughout, except for lengthening in QRS interval from an original measurement of 0.14 to 0.16 second. Although minor changes were observed in the T waves in the standard leads, there were no findings in these leads which were considered diagnostic of recent infarction. On the other hand, the precordial leads showed definite signs of recent infarction and furnished evidence of a different type of conduction defect from that postulated from the standard leads. In Lead V_6 there was an initial R wave, which reached its peak within 0.04 second, and a subsequent broad, slurred S wave, strongly suggestive of right bundle branch block. At first glance, the QRS complex of Leads V_1 through V_3 appeared to consist solely of a downward deflection; however, the time interval, as measured from the beginning of the QRS complex in Leads V_1 through V_3 to the end of the steep upstroke, was only 0.10 second, whereas the duration of the QRS complex, as measured in both the standard leads and Lead V_6 , was 0.14 second. More careful scrutiny of Leads V_1 through V_3 revealed an elevated, slurred plateau which, from measurements, was considered part of the R wave, the RS-T junction being marked by a slight dip. The findings in Leads V_1 through V_3 were transmitted from the right, rather than the left, side of the heart, as evidenced by the diphasic P waves, indicating proximity of the electrode to the right atrium and by the later attainment of the peak of the R wave in these leads than in Lead V_6 . Thus, the late, broad, slurred R wave detected by careful scrutiny of Leads V_1 through V_3 established the presence of right bundle branch block, and the initial Q wave in these leads was indicative of infarction of the interventricular septum. The pattern in Leads V_4 and V_5 differed significantly both from that in Leads V_1 through V_3 and from that in Lead V_6 . Although the transitional zone in right bundle branch block may be displaced as far to the left as V_4 or V_5 , the late R wave derived from the delayed activation of the outer wall of the right ventricle attains its maximum in Lead V_1 or V_2 and diminishes as the electrode is moved farther to the left. Thus, it was concluded that the late R wave in Leads V_4 and V_5 was of left, rather than right, ventricular origin. The normal P-R interval indicated that left, as well as right, bundle branch block could not be present, and the 0.04 second interval between the onset of the QRS complex and the beginning of the intrinsicoid deflection in Lead V_6 also excluded complete left bundle branch block. The initial Q wave and the subsequent prolonged slurred ascending limb of the R wave and postponement of the intrinsicoid deflection to 0.08 second in Leads V_4 and V_5 indicated that the conduction defect was in the anterolateral aspect of the outer wall of the left ventricle. From the Q-R pattern in Leads V_4 and V_5 , together with the elevated RS-T junction and cove-shaped inversion of the T wave in Lead V_4 , a diagnosis was made of anterolateral infarction, dense in the subendocardial layer and patchy in the mid-zone and subepicardial layer. The late R wave in Leads V_1 and V_2 , due to right bundle branch block, increased greatly in amplitude in the tracing of February 1, and the transitional zone shifted to

Woolsey, T. D., and Moriyama, I. M.: **Statistical Studies of Heart Disease. II. Important Factors in Heart Disease Mortality Trends.** Pub. Health Rep. 63:1247 (Sept. 24), 1948.

Difficulties in determining the death rate due to heart disease in the past forty years are discussed. Changes in the terminology, changes in the rules for selection of primary cause of death, and the inclusion of more and more states in the registration area, as well as the gradually increasing age of the population, makes statistical evaluation difficult. At any rate, since 1930 when the registration area was virtually complete, the mortality due to heart disease has definitely increased for every age group over 45 years of age but has remained the same or declined in all the younger age groups. Over 45 years of age, however, there has also been a compensating decrease in the mortality from a certain group of causes of death closely associated with heart disease, such as intracranial lesions of vascular origin, nephritis, arteriosclerosis, and hypertension. When this entire group of cardiovascular, renal, and senility patients is studied, there is no consistent trend of mortality rate. It is possible that a true increase may have occurred in the risk of dying from one or more of the various forms of heart disease, and a true decline may have occurred in the rate of dying from intracranial vascular lesions and chronic nephritis. The fact seems apparent that for the group of diseases which reflect damage to the heart, kidneys, and arterial system resulting from hypertension and arteriosclerosis, the basic risk of dying for a person over 35 years of age is neither rising nor falling.

WAIFE.

Laufman, H., Martin, W. B., and Tanturi, C.: **Effect of Heparin and Dicoumarol on Sludge Formation.** Science 108:283 (Sept. 10), 1948.

Using the technique of Kniseley, these authors during a course of vascular occlusion experiments in dogs were able to produce sludge at will and observe the result carefully. The sludge masses of blood cells may serve as a matrix for thrombus formation provided other conditions favorable to the development of thromboses are present. When anticoagulants are administered, thromboses do not generally occur in small vessels distal to an occlusion, but such doses do not prevent the formation of sludge.

The administration of anticoagulants prevents thrombus formation in the presence of sludge by preventing the sludged masses of cells from becoming adherent to the endothelial lining of the vessel. Sludge formation as such is not prevented.

WAIFE.

Rapport, M. M., Green A. A., and Page, I. H.: **Crystalline Serotonin.** Science 108:329 (Sept. 24), 1948.

These authors report the isolation from beef serum of a crystalline substance which is vasoconstrictor in effect and which appears in connection with platelet destruction and the clotting process. It has been provisionally named *serotonin*. Chemical analysis shows that it is a sulfate which may also contain organically bound sulfur. It gives a positive test for nitrogen and a negative test for the halogens.

Injected intravenously into anesthetized dogs and cats, a solution of this material produced a rise in arterial pressure which was augmented in a sympathectomized animal. In a few animals small doses produced a depressor effect which became a pressor effect after the administration of tetraethylammonium chloride. The response after pithing was slightly reduced or unchanged. When the perfused isolated rabbit ear preparation was used, the vasoconstrictor activity of serotonin was more than twice that of an equal weight of epinephrine hydrochloride.

WAIFE.

Prinzmetal, M. Corday, E. Bergman, H. C., Schwartz, L., and Spritzler, R. J.: **Radio-cardiography: A New Method for Studying the Blood Flow Through the Chambers of the Heart in Human Beings.** Science 108:340 (Sept. 24), 1948.

Using a device which is essentially a Geiger-Müller counter with a direct-writing attachment, Prinzmetal and his associates have been able to study the passage of radiosodium through

the cardiac chambers. They obtained curves which record the concentration of radiosodium in the structures underlying the pick-up tube which was placed over the precordium. Small doses which are nontoxic were used.

In the normal, a curve composed of two peaks was obtained. The first was produced when the radiosodium was in the right heart; this peak declined moderately while the radiosodium was primarily in the lungs. The second peak existed when the radiosodium was in the left heart; this gradually disappeared. In cardiac enlargement, with or without failure, almost all curves have been monophasic, that is, one peak and fall.

Other observations revealed that the rate of venous return from the lower limbs was much slower than that from the upper extremities, and when radiosodium was injected as an isotonic solution intramuscularly, one-half of the injected solution was absorbed in thirty minutes and 90 per cent in one hour. Thus, the time required for absorption was much longer than would be anticipated. In hemorrhagic shock in dogs, intramuscular absorption of radiosodium was greatly prolonged. Theoretical concepts were confirmed in a study of the tetralogy of Fallot in which the right and left waves took the form that was anticipated from physiological studies.

WAIFE.

Hurwitt, E. S.: An Experimental Approach to the Problem of Increasing the Blood Supply to the Lungs. Surg., Gynec. and Obst. 87:313 (Sept.), 1948.

The author describes an experimental technique to increase the blood supply to the lungs, particularly in the presence of pulmonary stenosis. Two avenues of approach were explored: (1) circumvention of the pulmonary valve by a shunt from the right ventricle to the proximal portion of the main pulmonary artery, and (2) dilatation of the pulmonary valve ring. In the shunt, polyethylene tubing was used. This is a chemically inert plastic substance which is light, malleable, flexible, easy to sterilize, and nonirritating to tissues. The experiments were performed upon eleven cats. Polyethylene tubing was successfully placed in three cats, although one died twelve hours postoperatively. One end of the pre-bent tube was sutured into the right ventricle, the other end into the pulmonary artery. Examination of two sacrificed cats showed no displacement of the ends of the tube. The lumen of the tube was occupied by a partially organized adherent thrombus. A thin fibrous membrane formed on the outer walls of the tube.

For dilatation of the pulmonary valve, the author used a tapered lucite prosthesis. This was inserted through an incision in the anterior wall of the ventricle of eight cats by a modified dura clip forceps. Three cats died immediately. In two cats the tube was not displaced; in one it migrated back to the ventricle, in one, to the bifurcation of the pulmonary artery, and in the third, to the hilus of the right lung.

The author suggests his experimental approach for the reproduction of the effects of valvular insufficiency and for the study of the altered physiology and dynamics of cardiac lesions.

BECK.

Barnes, C. G., Fatti, L., and Pryce, D. M.: Arterio-venous Aneurysm of the Lung. Thorax 3:148 (Sept.), 1948.

Arteriovenous aneurysm of the lung is usually considered to be a rarity, and by 1942 only four examples were on record. Nineteen additional cases have been published in the last six years, however, and it is likely that as the clinical features of this syndrome become better known, still more of these cases will be separated from the cases of cyanotic congenital heart disease and polycythemia rubra vera, with which they are often confused. Two cases of this disease are discussed.

The outstanding feature of this syndrome is intense cyanosis; increasing dyspnea on exertion is the second symptom of which these patients complain, and which eventually incapacitates them. This appears to be due to stimulation of the respiratory center by the high carbon dioxide content of the arterial blood. In addition to these symptoms, hemorrhage may also cause these patients to seek advice.

Among the clinical features is the presence of an arteriovenous shunt in the pulmonary circuit which may sometimes interfere with physical development. Cyanosis and clubbing are marked. Examination of the heart reveals no abnormality, the blood pressure is normal, and the electrocardiogram either is physiological or shows slight right axis deviation without ventricular strain. The lungs are normal unless the aneurysm is large and situated near the costal surface of the lung, in which case a systolic murmur may be heard over it, sometimes continuing into diastole. Further physical examination reveals no abnormality, but the absence of splenic enlargement is important and may be the first feature to throw doubt on a clinical diagnosis of polycythemia rubra vera. A radiograph shows the heart to be of normal size and contour, and the lung fields clear, except for the shadow caused by the lesion itself.

The authors point out that differential diagnosis is sometimes difficult, since there are four conditions with which pulmonary arteriovenous aneurysm may be confused: cyanotic congenital heart disease, Osler-Vaquez disease (polycythemia rubra vera), bronchiectasis, and pulmonary tuberculosis.

Arteriovenous aneurysm, not a true tumor but a developmental malformation (hamartoma), requires surgical treatment in the form of pneumonectomy, lobectomy, or local excision. No medical measures will prevent the development of increasing dyspnea, and serious complications may occur if surgery is not undertaken. Small aneurysms can be excised from the lungs by the application of clamps around the aneurysm in such a way as to close its main supplying vessel last, thus allowing its expansile pulsation to demonstrate its outline. In the case of large aneurysms, a lobectomy must be performed, with dissection and ligature of the hilar structures.

The circulatory changes produced by removal of the aneurysm do not embarrass the patient, and no special measures, such as venesection, are needed either before or after the operation. The red cell count returns to normal within a few weeks, and cyanosis lessens rapidly during the week after the operation.

BELLET.

Sorgo, W.: The Intramedullary Section of Vasomotor Pathways as Treatment of Arterial Hypertension. *Wien. med. Wchnscher.* 98:391 (Sept.), 1948.

In three patients suffering from essential hypertension a bilateral chordotomy as suggested by Foerster was performed. The operation consists of the resection of the vasomotor tracts at the level of low cervical or high thoracic segments. The pathways are supposed to be located in the middle of the anterolateral tract anterior to the pyramidal lateral area. Therefore, a deep section was made in the cord down to the gray matter. During or immediately following the operation the greatly elevated blood pressure fell considerably, in one instance to normal levels, to return to high figures within a few weeks or months. Disturbance of pain and temperature sensations made their appearance in all operated subjects.

BRUMLIK.

Jarisch, A., and Zotterman, Y.: Depressor Reflexes From the Heart. *Acta physiol. Scandinav.* 16:31 (Oct.), 1948.

In anesthetized cats nerve action potentials from afferent vagal nerve branches were recorded simultaneously with the electrocardiogram and with pressure changes within the right auricle. The recording system consisted of resistance-capacity coupled amplifiers for the nerve action potentials and balanced input amplifier for the electrocardiograms. A condenser placed in a high frequency circuit was used in recording intra-auricular pressures. Records were obtained by means of a multiple beam cathode ray tube. Slight traction excited auricular nerve endings which thus appeared to become active with each auricular contraction independent of auricular filling pressure although increasing intracavitary pressures were also followed by increased activity of these nerves, which resulted in cardiac slowing. The activity of the auricular branches could be separated from those serving ventricular muscle which on stimulation yielded smaller low voltage spikes. Their activity was greatly increased after clamping of the aorta or pulmonary artery. All fibers investigated appeared to have a high threshold to electrical stimulation (C fibers).

The response of blood flow to intramuscular adrenaline after sympathectomy was essentially the same as in the normal forearm. This was also the case with ephedrine. This suggests the action is largely peripheral. All of these substances seem to be able to bring about an active dilatation of the blood vessels in skeletal muscle, but, as with the action on the skin, adrenaline is the most effective.

Doses of adrenaline and ephedrine increase the cardiac output and apparently decrease the total peripheral resistance, adrenaline producing the larger effect in both instances. The results here described suggest that skeletal muscle is probably the main site of this decreased resistance. The greater dilatation observed with adrenaline than with ephedrine agrees with the greater decrease in total peripheral resistance after adrenaline and is probably a factor in the lowering of diastolic pressure by adrenaline, while ephedrine raises it. In general, the results show a very ready dilatation of muscle vessels by adrenaline, a much smaller dilatation by Methedrine, and an intermediate action by ephedrine.

These substances in those doses, which strongly dilate muscle vessels, lead to a considerable lowering of peripheral resistance and allow some acceleration of the heart, while no acceleration, or actual slowing, is found when the muscle dilatation is small. In general, the diastolic blood pressure is normal or low when muscle flow is high, and vice versa.

BELLET.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Low Blood Pressure in Diabetic Coma. Clin. Sci. 6:247 (No. 4), 1948.

It has long been recognized that in the later phases of diabetic coma the blood pressure may fall to low levels, and that this change is often irreversible, death following within a few hours. Efforts to raise the arterial pressure by drugs have been on the whole unsuccessful, while large intravenous infusions, given in the belief that the falling blood pressure was due to a diminished blood volume and a decreasing cardiac output, have frequently resulted in pulmonary edema.

The low blood pressure in diabetic coma is due to a decreased total peripheral resistance, which is below 50 per cent of the normal value. The site of the vasodilatation has not been determined. The cool, pale skin suggests that skin blood flow is diminished. Attempts to combat the peripheral vasodilatation by constrictor drugs have so far failed. The vasoconstrictor drugs, pitressin, digitalis, and d-N-methyl amphetamine hydrochloride (Methedrine), fail to raise the low arterial pressure, or show only a small transient effect. The vessels may show a transient initial constriction, but then appear to become insensitive to further injection of the drugs.

BELLET.

Cohen, S. M., Edholm, O. G., Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output and Peripheral Blood Flow in Arteriovenous Aneurysm. Clin. Sci. 7:35 (No. 1), 1948.

The observations were made on twelve patients. All were men and all had been wounded less than two years previously except two, Case 10, who had been wounded five years before, and Case 12, whose aneurysm had been present for twenty-nine years.

Cardiac output and right auricular pressure were studied by the technique of cardiac catheterization. Blood flow was measured in the forearm and in the leg by means of a venous occlusion plethysmograph. The arm was immersed in a water bath at 34° C., while the leg was in air at room temperature. Circulation through the aneurysm was shut off by digital pressure proximal to the aneurysm. In order to allow time for the circulation to reach a steady state, closure was maintained for one minute before the right auricular samples were withdrawn. Blood flow changes in the limbs were recorded within thirty seconds of closure of the shunt.

Cardiac output in liters per minute per 100 c.c. oxygen consumed was increased above the normal average of 2.2 in nearly all cases, the highest figure being 4.5 in a patient with a very large aneurysm. The venous filling pressure and heart rate were moderately increased. The increased cardiac output in large arteriovenous aneurysms has some relationship to the size of the communication. Closing the arteriovenous fistula by compressing the artery proximal to the shunt pro-

restored to normal by electrical stimulation was shown by the corresponding changes in circulation time from antecubital fossa to tongue, as illustrated in four subjects. The beneficial results were shown not to be the result of emotional disturbances consequent to the mild discomfort of the electrical treatment. The method is now being tried in the treatment of traumatic shock and as a preventive of postoperative shock, venous stasis, and thrombosis.

DURANT.

Hellems, H. K., Haynes, F. W. Dexter, L., and Kinney, T. D.: Pulmonary Capillary Pressure in Animals Estimated by Venous and Arterial Catheterization. *Am. J. Physiol.* 155:98 (Oct.), 1948.

Through the right and left ventricles small branches of the pulmonary artery and of the pulmonary veins were catheterized in anesthetized dogs. The tip of the catheter was wedged into distal branches of the artery and veins so that the lumina of the vessels were completely occluded. The average pressure in the blocked pulmonary artery branch was 6 mm. Hg (range 5 to 8 mm.), while the simultaneous pressure in the pulmonary vein was higher by approximately four mm. Hg (6 to 14 mm.). Pulmonary artery pressure averaged 31/14 mm. of mercury. The slight differences in pressures between distal artery and vein were explained by the reduction of blood flow locally at the obstructed artery, and by slight local passive congestion at the site of the occlusion of the pulmonary vein. The pulmonary capillary pressures could thus be interpreted as averaging about 8 mm. of mercury. The pressures were higher during expiration than during inspiration, but the arterial-venous difference was maintained.

Pulmonary hypertension was produced by injection of Lycopodium spores through a third catheter inserted into a branch of the pulmonary artery of the opposite lung. The resulting pulmonary infarction raised pulmonary artery pressure from 31/14 mm. Hg to 76/38 and caused a corresponding twofold rise in the distal pressures.

HECHT.

Hiatt, E. P.: Effects of Repeated Oral Doses of Quinine and Quinidine on the Blood Pressure and Renal Circulation of Dogs With Experimental Neurogenic Hypertension. *Am. J. Physiol.* 155:114 (Oct.), 1948.

Oral doses of quinine and quinidine (10 to 15 mg. per kilogram) were administered three times a day for several days to normal dogs and to four dogs with neurogenic hypertension. Plasma levels of 1.0 to 4.0 mg. per liter were obtained. In normal dogs renal plasma flow and glomerular filtration rate increased, without much change in blood pressure. In the hypertensive dogs renal circulation remained unchanged or actually increased, but a fall of blood pressure to near normal values was noted. Peripheral vasodilatation was thought to be the major cause of the pressure reduction. Quinidine depressed the blood pressure more than the quinine. The possibility that cardiac depression with lowered cardiac output may in part be responsible for the observed effects has not been excluded.

HECHT.

Williams, A. H., and Schroeder, H. A.: Asystolic Arterial Pressure Gradient as a Measure of Local Peripheral Resistance. *Am. J. Physiol.* 155:132 (Oct.), 1948.

The asystolic arterial pressure gradient was defined as the descending curve of intra-arterial pressure following sudden occlusion of a major artery. This gradient was measured in the brachial, femoral, renal, and mesenteric arteries of anesthetized dogs through an intra-arterial needle connected to a Hamilton manometer. In some experiments the systemic blood pressure was measured simultaneously from another artery, and blood flow determined by a recording rotameter. Collateral circulation was sometimes occluded by a tight wire tourniquet around the proximal portion of the limb. The period of occlusion was brief, usually 8 to 12 seconds.

With the inflow into the artery cut off, the blood volume in the arterial segment steadily diminished. This resulted in the typical pressure gradient curve which showed initially a very

rapid fall of pressure, followed by a more gradual but steady decline. There were local differences in that the renal and mesenteric arteries showed a more rapid early fall in pressure than did the femoral and brachial arteries. Changes in the slope of the curve were thought to correlate directly with local peripheral resistance, a steep slope indicating low, a slow slope high resistance of local areas of circulation.

When vasoactive drugs were injected, the pressure gradients were altered so that following an intravenous injection of epinephrin the gradient was lowered (the slope of the fall being more steep) and the blood flow increased, indicating vasodilatation. This was followed by a rise in the gradient and decreased blood flow to show vasoconstriction. The vasodilatation known to follow sodium nitrite injection was demonstrated by a fall in the gradient. The measurements were thought to be quantitative if the collaterals were cut off by the wire tourniquet.

HECHT.

Shapiro, R., and Rigler, L.: Pulmonary Embolism Without Infarction. Am. J. Roentgenol. 60:460 (Oct.), 1948.

Pulmonary embolism is now known to be a common complication of many diseases and operations. *The increasing frequency of diagnosis is probably due to better diagnostic criteria and to the greater attention which this condition is receiving.*

There is now sufficient clinical and experimental evidence to show that (in individuals with normal circulation) pulmonary embolism does not necessarily result in hemorrhagic infarction. In many of these cases, death ensues so rapidly that there is insufficient time for infarction to occur. There are, however, cases in which occlusion of a major pulmonary artery has been survived and with no evidence of infarction.

Westermarck, following prolonged roentgen studies with autopsy control, has concluded that hemorrhagic infarction does not occur unless there is an occlusion of both the bronchial and pulmonary arteries. If only the pulmonary artery is occluded, infarction does not follow and the involved segment remains viable even though it may be unable to carry on any exchange of gases. He found that only 20 per cent of the cases in which pulmonary embolism was established at autopsy showed an associated infarction. In spite of these findings most roentgenologists still associate pulmonary embolism with an area of increased density in the roentgenograms.

In pulmonary embolism without infarction, the characteristic finding is ischemia of the involved pulmonary segment. This is represented on the roentgenogram by a segmental area of increased radiability. Central to the site of the embolism, the vascular pattern is well defined while in the area involved there is an abrupt termination of the vascular pattern. Often there is a sharp demarcation between the involved and uninvolved segments. The occluded vessel sometimes shows increased density up to the point of abrupt termination. The emboli without infarction may undergo organization and recanalization and be reabsorbed (leading to re-establishment of the circulation in the involved segment) or result in a retrograde thrombosis producing a larger area of ischemic involvement.

The roentgen changes of pulmonary embolism without infarction must be differentiated from those of partial bronchostenosis with areas of obstructing and nonobstructing emphysema.

The authors present three autopsy-confirmed cases of pulmonary emboli without infarctions. The clinical findings were those of emboli and the roentgen findings were those of emboli without infarction. Other cases of a similar character were observed but not reported since the patients survived and autopsy confirmation could not be obtained.

ZION.

Kerr, W. J.: Pathogenesis of Rheumatic Fever. Ann. Int. Med. 29:587 (Oct), 1948.

The immunologic processes which are involved in rheumatic fever are not completely understood. Experiments concerning the development of auto-antibodies to various tissue extracts have suggested that the etiological agent, presumably the hemolytic streptococcus, by injury to or in combination with the connective tissues of the body produces auto-antibodies which act in vivo to bring about lesions in the living animal which may be progressive or may be reactivated by repeated exposure to the same organism. The reactions in the synovial membranes, subcutaneous tissues, cardiac valves, cardiac muscle, pericardium, lungs, and brain differ in the degree

Sigler, L. H.: Subjective Manifestations of the Hyperactive Carotid Sinus Reflex.
Ann. Int. Med. 29:687 (Oct.), 1948.

In 1,193 cases tested for hyperactivity of the carotid sinus reflexes, 970 (or 81.3 per cent) showed various subjective disturbances besides slowing of the heart rate and lowering of the blood pressure. In order of frequency, they consisted of dizziness, unconsciousness and convulsions, and abnormal sensation referable to the eyes, the vasomotor system, the sweat glands, the organs of sensation, the respiratory system, the somatic muscular system, the general constitutional state, the gastrointestinal system, and the heart. Individuals of the older age groups, especially those with cerebral arteriosclerosis, showed the greatest number and degree of disturbances. In some, the abnormalities occurred upon pressure on the carotid sinus of one side and not of the other. In others, the same abnormalities developed upon pressure on either one or the other side in the same patient but to different degrees. In still others, some symptoms developed with pressure on one side and other symptoms with pressure on the other. Unconsciousness and convulsions, with the associated manifestations due to the carotid sinus reflex, occurred in some of the patients who never had spontaneous attacks. Some patients gave a history of one or more attacks of spontaneous dizziness, fainting, or unconsciousness that was not due to demonstrable disease of the central nervous system but did not present these symptoms on carotid sinus pressure. Reflexes originating in other parts of the body presumably produced the same cerebral manifestations.

The underlying physiologic disturbances responsible for the various manifestations of the hyperactive carotid sinus reflex appear to occur in the central neurons or in efferent arms of the reflex arc, not in the carotid sinus receptors. For this reason, surgical removal of the nerve connections of the carotid sinus region cannot be expected to give relief in many cases, and whatever good results it may yield may not be permanent. It should be employed only in extremely serious cases of unconsciousness and convulsions which may be reproduced by the lightest pressure on the carotid sinus. Inasmuch as very serious complications may develop as a result of the test in individuals with cerebral arteriosclerosis, great caution must be used in performing the test in such individuals.

WENDKOS.

Cluxton, H. E., Jr., Bennett, W. A., and Kepler, E. J.: Anterior Pituitary Insufficiency (Panhypopituitarism—Simmonds' Disease), Pituitary Myxedema and Congestive Heart Failure (Myxedema Heart); Report of a Case and Findings at Necropsy.
Ann. Int. Med. 29:732 (Oct.), 1948.

Death in a 47-year-old man occurred following the relatively rapid development of severe congestive heart failure. During life, laboratory studies suggested the presence of thyroid and adrenal cortical insufficiency. Because of the neurological findings and a history of head injury, it was suspected that a post-traumatic atrophy of the pituitary gland was responsible for deficient formation of adrenotropic and thyrotropic hormones. An electrocardiogram showed low voltage of QRS and T-wave abnormalities in the limb leads, but not in the precordial leads. Necropsy revealed evidences of marked passive congestion in all organs as well as free fluid in the pleural, pericardial, and peritoneal cavities. Examination of the heart revealed dilatation and hypertrophy of the ventricles with interstitial fibrosis. There was no arteriosclerosis of the coronary arteries. The pituitary gland, the cortex of each adrenal gland, both lobes of the thyroid gland, and both testes were moderately atrophic. Hormonal factors were considered by the authors to be responsible for the structural changes in the heart and the subsequent myocardial failure.

WENDKOS.

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AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

Dr. Irvine H. Page, of Cleveland, has been elected President of The American Society for the Study of Arteriosclerosis. Other officers for the coming year are Dr. E. Cowles Andrus, Baltimore, Vice-president, and Dr. O. J. Pollak, Quincy, Mass., Secretary-Treasurer.

Directors elected are: (until 1952) Dr. Russell L. Holman, New Orleans, and Dr. Myron Prinzmetal, Los Angeles; (until 1951) Dr. Louis N. Katz, Chicago, and Dr. Henry S. Simms, New York; (until 1950) Dr. G. Lyman Duff, Montreal, and Dr. Joseph B. Wolffe, Philadelphia.

The Society, which will hold its annual meeting in Chicago on November 5-7 (see program in this issue), has prepared the following Statement of Policy:

The purpose of the American Society for the Study of Arteriosclerosis is to further research, to improve methods of diagnosis and treatment, to work toward prevention, and to disseminate reliable information relative to arteriosclerosis.

The membership is open to any scientist engaged in experimental or clinical research in the field of arteriosclerosis and related disorders. The Society seeks active cooperation with all organizations of similar aims or interested in related diseases and with any group which might be able to help in the solution of the urgent problem of arteriosclerosis.

ANNUAL MEETING OF THE GERONTOLOGICAL SOCIETY

The Annual Scientific Meeting will be held in Chicago, Nov. 5-7, 1949. The program has been arranged by Dr. William B. Kountz of St. Louis. On Monday, November 7, the session will be a joint one with the American Society for the Study of Arteriosclerosis.

SCIENTIFIC COUNCIL ELECTIONS

Dr. Tinsley R. Harrison, of Dallas, has been elected Chairman of the Scientific Council. This accords with the policy set a year ago to name as Chairman the immediate Past President of the American Heart Association. Dr. Harrison succeeds Dr. Arlie R. Barnes, of Rochester, Minn.

Dr. Carl J. Wiggers, Cleveland, was re-elected as Vice-chairman, and Dr. Lowell J. Rantz, San Francisco, was re-elected as Secretary.

Re-elected to the Executive Committee for three years are Dr. Kenneth G. Kohlstaedt, Indianapolis; Dr. Irvine Page, Cleveland; and Dr. Irving S. Wright, New York City. Re-elected to the Research Committee for five years are Dr. Ann G. Kuttner, New York City, and Dr. Lewis Thomas, New Orleans.

Dr. Harrison, Dr. Katz, Dr. George E. Burch (of New Orleans), Dr. Reno R. Porter (of Richmond, Va.), and Dr. John J. Sampson (of San Francisco), were named by the Council to one-year membership in the Assembly of the Association. Council members of the Board of Directors were noted in a previous issue.

REFRESHER COURSE PRESENTED AT UNIVERSITY OF VERMONT

A one-week refresher course for practicing physicians was conducted in June by the newly established Cardiovascular Unit of the University of Vermont Medical College. The course, comprising twenty-eight lectures, was presented at Bishop DeGoesbriand Hospital, in Burlington. Twelve faculty members participated and guest speakers were Dr. Paul D. White, of Boston, and Dr. *Mercier Fauteux, of Montreal.*

The Cardiovascular Unit began operations on July 1 and its investigative work is partly supported by funds from the National Heart Institute and the American Heart Association. Dr. W. Raab is its Director. Similar courses for postgraduate study are planned for the future for general practitioners in the northern New England area.

American Society for the Study of Arteriosclerosis

PROGRAM OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TO BE HELD IN

CHICAGO, ILL., NOV. 6-7, 1949

IN COOPERATION WITH THE GERONTOLOGICAL SOCIETY

November 6, 1949*

Morning

(Irvine H. Page, Presiding)

- 9:30- 9:40 Opening Session
- 9:40- 9:55 **Observations on the Experimental Production of Arteriosclerosis in the Guinea Pig**
Dorothy Nelson and A. C. Ivy, Department of Clinical Science, University of Illinois, Chicago, Ill.
- 9:55-10:00 Discussion
- 10:00-10:15 **Rapid Production of Atheromatosis in Rabbits**
O. J. Pollak, Quincy City Hospital, Quincy, Mass.
- 10:15-10:20 Discussion
- 10:20-10:35 **Modification of Experimental Atherosclerosis by Means of Intravenous Detergents**
Aaron Kellner, James W. Correll, and Anthony T. Ladd, Department of Pathology, Cornell University Medical College, New York, N. Y.
- 10:35-10:40 Discussion
- 10:40-10:55 **Studies on the Inhibition of Experimental Cholesterol Atherosclerosis in Alloxan Diabetes in the Rabbit**
G. Lyman Duff and Torrence P. B. Payne, Department of Pathology, McGill University, Montreal, Canada.
- 10:55-11:00 Discussion
- 11:00-12:00 **The Biology of Arterial Tissue**
Jerome Gross, Department of Biology, Massachusetts Institute of Technology, Cambridge, Mass.
- 12:00-12:15 Discussion

Afternoon

(E. Cowles Andrus, Presiding)

- 2:00- 2:30 Business Session
- 2:30- 2:45 **Serum Lipids in Canine Arteriosclerosis**
Jack D. Davidson, Liese Lewis Abell, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.
- 2:45- 2:50 Discussion
- 2:50- 3:05 **The Pathology of Early Lesions in Experimental Canine Arteriosclerosis**
Margaret Bevans, Jack D. Davidson, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.
- 3:05- 3:10 Discussion

*The Gerontological Society will meet in an adjoining room.

- 3:10- 3:25 **Vascular Lesions in the Dog Following Thyroidectomy and Viosterol Feeding**
W. B. McAllister and L. L. Waters, Yale University, New Haven, Conn.
- 3:25- 3:30 Discussion
- 3:30- 3:45 **The Relationship of Blood and Liver Cholesterol to Atherosclerosis in Different Species**
H. J. Deuel, Jr., W. Marx, R. Alfin-Slater, and L. Marx, University of Southern California Medical School, Los Angeles, Calif.
- 3:45- 3:50 Discussion
- 3:50- 4:05 **Vascular Lesions in Experimental Hypertension**
A. C. Corcoran, Georges Masson, Beech Hazard, and Irvine H. Page, Research Division and Department of Pathology of the Cleveland Clinic Foundation, Cleveland, Ohio.
- 4:05- 4:10 Discussion
- 4:10- 4:25 **Histologic Sequence of Degeneration and Repair of the Rabbit Aorta Following Hypothermal Injury**
Bruce Taylor, David Baldwin, and George M. Hass, Rush Department of Pathology, Presbyterian Hospital, Chicago, in affiliation with the Department of Pathology, University of Illinois College of Medicine, Chicago, Ill.
- 4:25- 4:30 Discussion
- 4:30- 4:50 **Development and Metamorphosis of Cholesterol-Induced Atherosclerosis in the Chick. Effects of a Restricted Dietary Intake and of Cessation of Cholesterol Feeding**
L. N. Katz, L. Horlick, S. Rodbard, J. Stamler, and C. Bolene, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

November 7, 1949

Morning

(G. Lyman Duff, Presiding)

- 9:30- 9:40 Opening Session
- 9:40- 9:55 **Further Studies on the Action of Antilipfanogen in Preventing Fat Deposition**
Henry S. Simms, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 9:55-10:00 Discussion
- 10:00-10:15 **The Etiology of Coronary Sclerosis in Chickens**
J. C. Paterson and G. E. Cottral, Department of Medical Research, University of Western Ontario, London, Canada, and the Regional Poultry Research Laboratory, United States Department of Agriculture, East Lansing, Mich.
- 10:15-10:20 Discussion
- 10:20-10:40 **Studies on Spontaneous and Cholesterol-Induced Atherosclerosis and Lipid Metabolism in the Chick. The Effects of Some Lipotropic and Hormonal Factors**
J. Stamler, C. Bolene, L. N. Katz, R. Harris, E. N. Silber, A. J. Miller, and L. Akman, Cardiovascular Department, Medical Research Institutè, Michael Reese Hospital, Chicago, Ill.
- 10:40-10:45 Discussion
- 10:45-11:00 **Experimental Atheromatosis and Athero-hepatosis in Ducks and Geese; Its Reversibility and Clinical Implication**
Joseph B. Wolffe, Victor A. Digilio, Anthony D. Dale, George E. McGinnis, Daniel J. Donnelly, Mikhail B. Plungian, Joseph Sprowls, Frederick James, Claire Einhorn, and George Werkheiser, Wolffe Clinic and Hospital and Research Department, School of Pharmacy, Temple University, Philadelphia, Pa.
- 11:00-11:05 Discussion

- 11:05-11:20 **Simultaneous Studies on the Serum Lipids and the Electrophoretic Pattern of the Serum Protein in Man: Action of Inositol and Other Substances**
Irving Leinwand and Dan H. Moore, Department of Medicine, Post-Graduate Medical School of the N. Y. U.-Bellevue Medical Center and the Electrophoresis Laboratory, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 11:20-11:25 Discussion
- 11:25-11:40 **The Vascular Problem in Diabetes Mellitus**
R. S. Megibow, H. Pollack, S. J. Megibow, J. J. Bookman, and K. Osserman, Mount Sinai Hospital, New York, N. Y.
- 11:40-11:45 Discussion
- 11:45-12:00 **Changes in the Cutaneous Arterioles in the Arm and Leg in Coarctation of the Aorta**
Edgar A. Hines, Jr., Eugene M. Farber, and Norman M. Keith, Mayo Clinic, Rochester, Minn.
- 12:00-12:05 Discussion

Afternoon

(Louis N. Katz, Presiding)

- 2:00- 2:15 **Does Arteriosclerosis Develop by Episodic Stages?**
Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.
- 2:15- 2:20 Discussion
- 2:20- 2:35 **The Use of Radioactive Sodium in Evaluating the Peripheral Circulation in Peripheral Arteriosclerosis**
Beverly C. Smith, New York, N. Y.
- 2:35- 2:40 Discussion
- 2:40- 2:55 **Prognosis in Abdominal Aortic Aneurysm**
J. Earle Estes, Mayo Clinic, Rochester, Minn.
- 2:55- 3:00 Discussion
- 3:00- 3:15 **Nature of the Hyaline Material in Arteriosclerosis of the Kidney**
Roger D. Baker and Sidney P. Kent, Department of Pathology, Medical College of Alabama, Birmingham, Ala.
- 3:15- 3:20 Discussion
- 3:20- 3:35 **The Principal Syndromes Associated With Cerebral Arteriosclerosis**
Frederic D. Zeman, Medical Department, The Home for Aged and Infirm Hebrews, New York, N. Y.
- 3:35- 3:40 Discussion
- 3:40- 3:55 **Results of Treatment of Coronary Arteriosclerosis With Choline**
Lester M. Morrison and William F. Gonzalez, Los Angeles, Calif.
- 3:55- 4:00 Discussion
- 4:00- 4:15 **Fat Absorption and Atherosclerosis: A Theory on the Development of Atherosclerosis With Ageing***
H. Necheles, Jacob Meyer, and G. H. Becker, Department of Gastro-Intestinal Research, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.
- 4:15- 4:20 Discussion
- 4:20- 4:35 **The Effect of Estrogens Upon the Partition of the Serum Lipids in Female Patients**
Mary Lou Eilert, University of Chicago, Chicago, Ill.
- 4:35- 4:40 Discussion
- 4:40- 5:00 Closing Session

*May be presented in a Symposium on Nutrition at the Gerontological Society Meeting, November 5.

TO BE READ BY TITLE

Histology of Infarcted Heart Muscle

Rudolf Altschul, University of Saskatchewan, Saskatoon, Canada

Thyroid Activity and Tissue Cholesterol Distribution

Walter Marx and Lore Marx, Department of Biochemistry, University of Southern California, School of Medicine, Los Angeles, Calif.

The Hamster as Experimental Animal for the Study of Atheromatosis

J. Goldman and O. J. Pollak, Quincy, Mass.

A Method for the Estimation of 7-Ketocholesterol in Serum

Forrest E. Kendall, Walter Meyer, and Jack D. Davidson, Goldwater Memorial Hospital, New York, N. Y.

A Study of Atherosclerosis in Diabetes Mellitus

Joseph I. Goodman, Sigmund Wasserman, Louis J. Marcus, and Leonard Frankel, Mount Sinai Hospital, Cleveland, Ohio

Glomerular Obsolescence in Arteriosclerosis; Identity and Significance

J. F. A. McManus, Medical College of Alabama, Birmingham, Ala.

Aging As a Factor in the Renal Hemodynamic Response to a Standardized Pyrogen Test

Roger K. McDonald, David H. Solomon, and Nathan W. Shock, Section on Cardiovascular Disease and Gerontology, National Institutes of Health, Bethesda, Md., and Baltimore City Hospitals, Baltimore, Md.

The Silica Content of the Aortic Wall in Arteriosclerosis

E. Kirk and S. A. Kvorning, Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Metabolic Studies in Coronary Thrombosis

Lester M. Morrison, Albert L. Chaney, William Gonzalez, and Perla Berlin, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

Fat Tolerance Tests in Coronary Thrombosis

Lester M. Morrison, Perla Berlin, and William F. Gonzalez, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

The Significance of Blood Serum Cholesterol Instability in Coronary Arteriosclerosis

Lester M. Morrison, Lillian Hall, and William F. Gonzalez, Los Angeles County General Hospital and the Department of Internal Medicine of the College of Medical Evangelists

The Effect of Crude Renal Extracts and Purified Renin on Vascular Lesions in Experimental Malignant Renal Hypertension

R. O. Burns, Jr., W. H. Jasper, and G. E. Wakerlin, Department of Physiology, University of Illinois College of Medicine, Chicago, Ill.

Fat Tolerance Curves in Rat and Rabbit Using I¹³¹

G. Masson, O. Glasses, K. Savard, A. C. Corcoran, and Irvine H. Page, Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio

The Effect of Graded Dosages of Iodide on Plasma and Liver Cholesterol of Normal, Cholesterol-Fed and Thyroidectomized Rabbits

Helen Bennett Brown and Irvine H. Page, Research Division and the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Cleveland, Ohio

PROCEEDINGS OF THE AMERICAN SOCIETY FOR THE
STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

OBSERVATIONS ON THE EXPERIMENTAL PRODUCTION OF
ARTERIOSCLEROSIS IN THE GUINEA PIG

DOROTHY NELSON AND A. C. IVY, CHICAGO, ILL.

Department of Clinical Science, University of Illinois

There is at least one unidentified factor that is an essential nutrient for the guinea pig, in the absence of which these animals fail to grow, and die prematurely. If inadequate amounts of the factor are supplied, the guinea pigs survive for many months but develop severe pathologic changes, including arteriosclerosis.

Yeast, dried grass, and milk are thought to contain the unidentified factors (Elvehjem). Diets containing 30 per cent casein, 20 per cent cellulose, yeast, cerophyl, and liver extract promote good growth (Wooley). Crude casein contains a factor that increases growth and survival of pigs and which cannot be replaced by vitamin-free casein plus an excess of all the vitamins known in 1943 (King).

Our diet included all of these suggested factors for optimal development of the guinea pig. The cellulose in our diet was Ruffex. Recently Elvehjem and associates have found that gum arabic as 15 per cent of the diet is far superior to other forms of bulk and permits the reduction of casein to 20 per cent.

Arteriosclerosis develops slowly and most of our guinea pigs did not live long enough to manifest the condition. In some, however, the lesions were so advanced that they could be seen grossly and even palpated. The condition is not confined to the aorta. All of these pigs show liver, kidney, and adrenal damage together with damage of supporting tissues.

RAPID PRODUCTION OF ATHEROMATOSIS IN RABBITS

O. J. POLLAK, QUINCY, MASS.

Quincy City Hospital

Colloidal cholesterol suspensions dispersed in partially deproteinized rabbit's serum were injected intravascularly into rabbits.

Subintimal cholesterol deposits were observed immediately upon completion of injection of 65 mg. of fine suspension or as little as 5.0 mg. of coarse cholesterol suspension. Injection of larger amounts of cholesterol or modification of the volume of vehicle injected did not influence the results of experiments. Vascular alterations were seen in arteries of all calibers and also in veins; localization of lesions depended largely upon the site of injection.

While rabbits sacrificed immediately after injection showed numerous vascular alterations, animals examined sixteen hours after injection showed but few lesions. The number of atheroma-like lesions dropped to about one-tenth in rabbits allowed to survive for seven days after injection. Week-old plaques showed invasion with fibroblasts.

The lesions were larger upon injection of coarse suspension than when fine dispersed cholesterol was introduced. The number of plaques increased with multiple injections, as did the number of organized lesions.

Our observations suggest (1) that the initial lesions of experimental atheromatosis are due to intravascular precipitation of colloidal particles, (2) that these alterations are to a large extent reversible, (3) that resorption starts in about sixteen hours, (4) that subintimal deposits which are not resolved organize within approximately seven days, (5) that multiple episodes of dyscholesterolemia (a term used to characterize the dyscolloid state of cholesterol) have a cumulative effect. Vascular alterations produced by injection of colloidal graphite are indistinguishable from those initiated by injection of colloidal cholesterol. This suggests that atheromatosis is the result of a colloidal phenomenon, a nonspecific foreign body reaction in which intimal endothelial cells act as phagocytes.

MODIFICATION OF EXPERIMENTAL ATHEROSCLEROSIS BY MEANS OF INTRAVENOUS DETERGENTS

AARON KELLNER, JAMES W. CORRELL, AND ANTHONY T. LADD,
NEW YORK, N. Y.

Department of Pathology, Cornell University Medical College

The intravenous injection of the detergents Tween 80 or Triton A-20 into rabbits maintained on a cholesterol-free diet resulted in marked elevation of blood cholesterol and phospholipid levels and in the development of visible lipemia. It was possible by means of repeated intravenous injections of these detergents to sustain the elevated blood cholesterol and phospholipid levels for as long as twelve weeks. The blood phospholipid content rose parallel with the cholesterol in all cases.

The repeated intravenous injection of either Tween 80 or Triton A-20 into rabbits fed a high-cholesterol diet retarded or prevented the development of atherosclerosis. Groups of rabbits were fed a high-cholesterol diet and received Tween 80 twice daily or Triton A-20 twice weekly for nine to twelve weeks by intravenous injection. Control animals were fed the same cholesterol diet but received no intravenous detergents. The rabbits fed cholesterol and given intravenous detergents had far higher mean levels of blood cholesterol than the control animals, but significantly less atherosclerosis. The blood phospholipid levels of these animals were elevated in the same range as the cholesterol, whereas in the control animals phospholipid concentrations were invariably much lower than those of cholesterol. The incidence and severity of atherosclerosis was decreased if the blood phospholipid content was elevated concomitantly with the cholesterol. These studies suggest that the level of blood phospholipids may be an important factor in the development of experimental atherosclerosis.

Intravenous detergents were ineffective in the resorption of atherosclerosis previously produced by cholesterol feeding.

STUDIES ON THE MECHANISM OF THE INHIBITION OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN ALLOXAN DIABETES IN THE RABBIT

G. LYMAN DUFF AND TORRENCE P. B. PAYNE, MONTREAL, CANADA

Department of Pathology, Pathological Institute, McGill University

It has been previously shown by Duff and McMillan that the development of experimental cholesterol atherosclerosis is inhibited in alloxan diabetes in the rabbit. Two factors were observed to be consistently associated with this inhibition: the diabetic state and a degree of visible lipemia considerably greater than that observed in the control animals.

In an attempt to elucidate the mechanism of this inhibitory effect, the serum lipids were studied in normal and alloxan diabetic rabbits before and during the process of cholesterol feeding. One portion of each sample of serum was extracted with alcohol-ether for the determination of neutral fat and lipid phosphorus, and another with acetone-absolute alcohol for the determination of free and total cholesterol content. These represented absolute values. Another portion was dried from the frozen state in vacuo and extracted with cold chloroform, as described by Forbes and co-workers, and the content in this extract of neutral fat, lipid phosphorus, and free and total cholesterol determined. The lipids extracted in this way are referred to as the "readily extractable fractions" and are considered to represent lipids not bound, or only loosely bound, to the serum proteins.

It was found that in the transitory hyperlipemia which may occur in the early stages of alloxan diabetes in the rabbit, all of the serum lipid constituents, but especially the neutral fat, were elevated. When cholesterol was fed following the subsidence of the spontaneous lipemia, there occurred an elevation of all the serum lipid constituents in both the normal and the diabetic rabbits. In the diabetic rabbits, however, the neutral fat showed a much greater rise in proportion to the increase in total cholesterol than it did in the normal rabbits.

In the normal animals the proportions of "readily extractable" lipid phosphorus and cholesterol were small while most of the neutral fat was "readily extractable." As the lipids became elevated during cholesterol feeding the "readily extractable fractions" tended to approximate the absolute lipid values in both the normal and the diabetic rabbits, although the approximation was somewhat more marked in the diabetics, that is a greater proportion of neutral fat was "readily extractable" in the diabetic rabbits than in the normal rabbits.

The factor that appeared to be most consistently associated with the inhibitory effect of alloxan diabetes on the development of experimental cholesterol atherosclerosis in the rabbit was the presence in the sera of the diabetic animals of a greater proportion of neutral fat in proportion to the level of cholesterol than in the normal control rabbits. It is suggested that the greater elevation of neutral fat in the cholesterol-fed diabetic rabbits is connected with mobilization of body fat associated with the diabetic state.

THE BIOLOGY OF ARTERIAL TISSUE

JEROME GROSS, BOSTON, MASS.

Department of Biology, Massachusetts Institute of Technology, Cambridge, and Department of Medicine, Massachusetts General Hospital

The present paper will concern itself with one phase of the above-assigned title, namely the fine structure analysis of the components of arterial tissue. Among the constituents of the arterial wall, collagen, reticulin, and elastin have been intensively studied to date from the viewpoint of their macromolecular organization. The smooth muscle, endothelium, and cement substances have thus far received scant attention.

Collagen fibers are composed of bundles of fibrils whose diameters are below the resolving power of the light microscope. As seen with the electron microscope, these fibrils have a complex, axial repeating pattern with a period of 640 Angstrom units, which appears to be constant for collagen from all tissues of all the species of animals studied thus far. The collagen fibril itself is a parallel bundle of still thinner filaments bonded together laterally in a manner not yet fully understood. The strength of this lateral bonding appears to vary in different

tissues. The argyrophilic reticulin of the newborn rat aorta and rat skin appears to have the same characteristic cross-banded fibrils as does adult collagen, although these fibrils are considerably smaller in diameter.

Recent electron microscope studies of aortic elastic tissue have revealed large, branching fibers which are composed of bundles of trypsin-resistant, helically coiled threads imbedded in a trypsin-sensitive binding matrix. This general structure seems to be characteristic also of the elastin of other tissues. Inferences concerning the macromolecular architecture of elastic tissues may be drawn from physical properties such as thermoelasticity and force-extension relations. This aspect will be briefly discussed.

The possibilities and limitations of some of the biophysical techniques employed in a study of arterial tissue will also be discussed.

SERUM LIPIDS IN EXPERIMENTAL CANINE ARTERIOSCLEROSIS

JACK D. DAVIDSON, LIESE LEWIS ABELL, AND FORREST E. KENDALL,
NEW YORK, N. Y.

Goldwater Memorial Hospital

Most of the cholesterol in serum is not in true solution but is present in colloidal form, presumably stabilized by the phospholipids and serum proteins. Changes in the phospholipid-cholesterol ratio may be as important as hypercholesterolemia in the development of experimental arteriosclerosis. Therefore, data on the serum levels of free and total cholesterol, total lipids, and lipid phosphorus have been obtained on more than forty dogs on a regimen of thiouracil-cholesterol feeding.

Each dog was given 0.6 Gm. thiouracil daily and was fed a ration containing 5 per cent cholesterol *ab lib*. Blood samples were taken every two weeks for lipid determinations. Most of the dogs attained serum cholesterol levels of 1,000 mg. per cent or over within the first two weeks of the regimen and maintained high levels as long as it was continued. Values up to 5,000 mg. per cent were observed. A rise in total lipids and lipid phosphorus also occurred, but to a less marked degree.

In fifteen young dogs on a normal diet, the molar ratio of cholesterol and phospholipid was approximately 1:1. Following cholesterol-thiouracil feeding, the phospholipid increased at the average rate of one mol of phospholipid for every 5 mols of cholesterol.

Upon discontinuance of the thiouracil and cholesterol the serum levels of all the lipids declined at parallel and approximately exponential rates, reaching normal levels within one week.

THE PATHOLOGY OF EARLY LESIONS IN EXPERIMENTAL CANINE ARTERIOSCLEROSIS

MARGARET BEVANS, JACK D. DAVIDSON, AND FORREST E. KENDALL,
NEW YORK, N. Y.

Goldwater Memorial Hospital

The efforts of the past year were designed to determine the length of time and the degree of elevation of serum cholesterol necessary to produce arteriosclerotic lesions in dogs on the thiouracil-cholesterol regimen and to study the sequence of histologic changes occurring in the formation and regression of the plaque.

In the dogs examined thus far, the degree of arteriosclerosis produced closely parallels the height and duration of the cholesterolemia maintained. It has been found that dogs sacrificed after two months of marked hypercholesterolemia

have macroscopic plaques especially marked in the thyroid arteries. Microscopic examination revealed these plaques to be due chiefly to accumulation of lipid in the media. Although the intima was laden with lipid, no proliferation of intimal cells was present. In dogs sacrificed after four months there were more widespread lesions showing beginning intimal proliferation, particularly in the arteries of the cephalad part of the body. In dogs sacrificed after six months the lesions were consistently more widespread and intimal proliferation was definite. In these latter dogs the arteries of the lower limbs were strikingly involved and there were indications that lesions in the fore part of the body had regressed despite continued hypercholesterolemia.

A number of dogs have been placed on a normal diet after a period of thiouracil-cholesterol feeding. Animals sacrificed at intervals of two to five months after their serum cholesterol levels returned to normal showed intimal proliferation as well as persistence of lipid in both intima and media in some arteries. In other arteries histologic evidence of regression of the plaque was thought to be present.

VASCULAR LESIONS IN THE DOG FOLLOWING THYROIDECTOMY AND VIOSTEROL FEEDING

W. B. McALLISTER AND L. L. WATERS, NEW HAVEN, CONN.

Yale University

The arterial changes that follow thyroidectomy and the feeding of large quantities of viosterol have been reinvestigated. Widespread lesions of the aorta and coronary arteries appear in three weeks. The distribution of the aortic lesions duplicates that of intimal aortic sclerosis in man. The coronary arteries are regularly involved. The location of these lesions within the arterial wall is as often intimal as medial. Edema, hemorrhage, necrosis, and cellular inflammatory exudates are prominent components. Stainable lipid is present in many of the lesions, sometimes in association with acute inflammatory foci and sometimes in association with deposits of calcium salts. This lipid can be demonstrated after a few weeks of feeding. It is actively phagocytized. Accumulations of fat-laden foam cells appear in the intima of the affected vessels. Some degree of diffuse renal damage is regularly present.

The results of chemical examination of blood constituents (including lipids) of the experimental animals will be presented, and the significance of the morphologic and chemical findings briefly discussed.

THE RELATIONSHIP OF BLOOD AND LIVER CHOLESTEROL TO ATHEROSCLEROSIS IN DIFFERENT SPECIES

H. J. DEUEL, JR., W. MARX, R. ALFIN-SLATER, AND L. MARX,
LOS ANGELES, CALIF.

University of Southern California Medical School

The plasma and liver cholesterol levels and the histologic response of the aortas of rabbits, chickens, hamsters, guinea pigs, and rats were determined after the feeding of diets high in cholesterol for ten to sixteen weeks. Rabbits and chickens had the highest plasma cholesterol content while the cholesterol deposition in the liver of the hamsters far exceeded that of any other species. Significant cholesterol deposition and atherosclerosis occurred only in the rabbit and chicken while no evidence of such changes was found in the other groups. There appears to be no relation between liver cholesterol and susceptibility to atherosclerosis. Studies are being made on the relative rates of cholesterol turnover in different species with deuterium being used as a tracer.

VASCULAR LESIONS IN EXPERIMENTAL HYPERTENSION

A. C. CORCORAN, GEORGES MASSON, BEECH HAZARD, AND IRVINE H. PAGE,
CLEVELAND, OHIO

Research Division and Department of Pathology, Cleveland Clinic Foundation

Hypertension was produced in rats by silk perinephritis, by administration of desoxycorticosterone acetate (DOCA) and by injection of a suspension of lyophilized anterior pituitary (AP). Rats given DOCA and AP were female, unilaterally nephrectomized, and they received 1 per cent sodium chloride as drinking water. Rats of the AP series were given a high-protein diet. Blood pressures were measured at regular intervals and the course of the hypertension was related to the vascular lesions.

It was shown: (1) That the lesions are similar in the three types of hypertension. (2) That lesions were present in all hypertensive animals and in some normotensive animals in the renal and DOCA groups. (3) That the type of lesion varies with the site; necrotizing panarteritis predominates in the mesenteric vessels; the heart shows either perivascular proliferation of reticulum cells with formation of granuloma or perivascular aggregations of cells with deeply staining nuclei and poor cytoplasm, the latter lesion resembling an Aschoff body; the kidneys show glomerulitis and arteriolonecrosis. (4) With DOCA, the first lesion is an accumulation of cells in the stroma of pancreas and mesentery. This appears when the rise in blood pressure is beginning.

HISTOLOGIC SEQUENCES OF DEGENERATION AND REPAIR OF THE RABBIT AORTA FOLLOWING HYPOTHERMAL INJURY

C. BRUCE TAYLOR, DAVID BALDWIN, AND GEORGE M. HAAS, CHICAGO, ILL.

Rush Department of Pathology, Presbyterian Hospital, Chicago, in affiliation with Department of Pathology, University of Illinois College of Medicine

Local lesions were produced in aortas of juvenile and senile rabbits with a hypothermal instrument cooled with expanding carbon dioxide. Animals were sacrificed at intervals during a period of twenty-four weeks thereafter and lesions were studied microscopically in serial sections. Degenerative and regenerative responses manifested a constantly changing pattern.

Aneurysmal dilatation occurred immediately after lesions were produced; inflammatory reaction was insignificant. Degeneration of smooth muscle cells in the media was apparent one week after injury and complete at two weeks. Elastic lamellae became straight, fused, and fragmented two weeks after injury. Medial calcification first appeared three weeks after injury and was complete at five weeks. In juvenile rabbits calcium in the media was slowly reabsorbed; in senile rabbits cartilage and bone replaced the calcium. Lesions of juvenile rabbits, after six weeks, were contracted; those of senile rabbits still showed aneurysmal dilatation.

Proliferation of the intima began in all animals at two weeks and was complete at five weeks. In juvenile rabbits the quantity of intimal proliferation was much greater than in senile rabbits. New formation of elastic tissue was observed in all animals in the thickened intima in lesions three weeks old. After twenty-four weeks, elastic fibrils in the proliferated intima resembled those of normal medial elastic lamellae. In all animals smooth muscle cells appeared in the thickened intima at two weeks. At six weeks they were as abundant and mature as those in normal media.

At four weeks, in all rabbits, a new internal elastic membrane began to form and was almost completely formed at twenty weeks. Since proliferated intima provided a matrix for new elastic tissue lamellae and smooth muscle cells, quantities of all elements were much greater in juvenile rabbits. Essentially, a new vessel wall developed within the framework of the proliferated intima.

DEVELOPMENT AND METAMORPHOSIS OF CHOLESTEROL-INDUCED ATHEROSCLEROSIS IN THE CHICK. EFFECTS OF A RESTRICTED DIETARY INTAKE AND OF CESSATION OF CHOLESTEROL FEEDING

L. N. KATZ, L. HORLICK, S. RODBARD, J. STAMLER, AND C. BOLENE,
CHICAGO, ILL.

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

A study was undertaken to determine the physiologic parameters and preconditions of reversibility of avian cholesterol-induced atherosclerosis. For this purpose 5- to 8-week-old cockerels were fed 2 per cent cholesterol and 20 per cent cottonseed oil for ten weeks. Extensive atherosclerosis of the great vessels was observed in birds sacrificed at this time. Three groups were permitted to survive for another fourteen weeks on diets of (a) 2 per cent cholesterol and 20 per cent oil, (b) defatted chick starter mash, or (c) regular starter mash.

Continuous cholesterol feeding over a twenty-four-week period resulted in a sustained hypercholesterolemia and increasingly severe aortic atherosclerosis. Microscopic studies showed increasingly heavy deposits of fat and cholesterol in the intima and media of the aorta, atheromatous "abscesses," and calcification. Cessation of cholesterol feeding resulted in a fall of the blood cholesterol to normal values within two to three weeks and a gradual diminution of grossly visible atherosclerotic lesions in both the low-fat (b) and normal (c) categories. There was no significant difference between the two groups. There was a marked tendency toward resorption of the less severe atherosclerotic lesions, with productive fibrotic and calcific changes in the more severe lesions.

The effect of a limited dietary intake (semistarvation) on lipid metabolism and atherogenesis was also investigated by giving a series of cockerels a diet approximately 50 per cent of that taken *ad lib* by a control group. This limited diet was supplemented with 4 per cent or 8 per cent cholesterol. On this diet growth and development were markedly retarded.

Serial plasma lipid fractionations revealed that these chicks, despite a grossly inadequate caloric intake, had a sustained hyperlipemia involving all elements, including cholesterol, phospholipids, and fatty acids. Correlated with this was a marked liver lipidosis and a high incidence of severe atherosclerosis of the aorta.

It is concluded from these studies that: (1) Under certain conditions atheromatous lesions are reversible. (2) In the chick, hyperlipemia and atherogenesis are dependent to a large degree upon the amount of ingested cholesterol; even conditions of relative starvation will not reverse these effects of dietary cholesterol.

FURTHER STUDIES ON THE ACTION OF ANTILIPFANOGEN IN PREVENTING FAT DEPOSITION

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THE ETIOLOGY OF CORONARY SCLEROSIS IN CHICKENS

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The evidence is reviewed that the primary lesion in coronary sclerosis of chickens is a focus of cellular infiltration and degeneration of the medial coat of the artery. The cause of the primary medial lesion has been sought, and the results of the various investigations are reported here.

Cholesterol feeding, infectious disease of an acquired type, and hypersensitivity to dietary agents have all been studied; but none of these appears to be of importance in the initiation of the primary lesion. On the other hand, evidence has been obtained which suggests strongly that the primary lesion of coronary sclerosis in chickens is a manifestation of lymphomatosis.

STUDIES ON SPONTANEOUS AND CHOLESTEROL-INDUCED ATHERO-
SCLEROSIS AND LIPID METABOLISM IN THE CHICK.
THE EFFECTS OF SOME LIPOTROPIC
AND HORMONAL FACTORSJ. STAMLER, C. BOLENE, L. N. KATZ, R. HARRIS, E. N. SILBER,
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The combined effects of 1 per cent choline and 1 per cent inositol on lipid metabolism and on spontaneous and cholesterol-induced atherosclerosis were observed in cockerels over the course of twenty-five weeks. The lipotropic factors tended to aggravate the hyperlipemia and hypercholesterolemia and exerted a moderate, incomplete lipotropic effect on the fatty livers of cholesterol-fed chicks. Choline and inositol did not prevent, and actually tended to aggravate, aorta lipidosis and atherosclerosis in cholesterol-fed chicks. In chicks fed regular mash, they had no effect on lipid levels and did not prevent early (six months) spontaneous atherosclerosis.

Pancreatectomized chicks fed regular mash exhibited no alteration in plasma lipid levels, and at fifteen weeks were free of spontaneous atherosclerosis. Cholesterol-fed pancreatectomized chicks exhibited alterations in plasma and organ lipids and in atherogenesis similar to unoperated birds given cholesterol. Apparently removal of the pancreas in the chick does not lead to the marked derangements in lipid metabolism and to the early vascular lesions observed in man.

The effects of thyroid and dinitrophenol on chick lipid metabolism and atherogenesis were compared in an attempt to clarify the mechanism of thyroid inhibition of cholesterol-induced hyperlipemia and atherosclerosis. Unlike thyroid, dinitrophenol had no consistent effect on plasma lipid levels nor on the frequency or extent of atherosclerosis in the cholesterol-fed chicks. It appears that the specific biochemical chain of events affected by thyroid hormone, and not hypermetabolism in general, is essential to alter lipid metabolism and atherogenesis in cholesterol-fed birds.

In chicks on regular mash, early spontaneous aortic atherosclerosis was observed as early as the fifteenth week of feeding either thyroid or dinitrophenol. Thus, unlike its effect on cholesterol-forced atherosclerosis, thyroid does not prevent, and may even aggravate, spontaneous atherosclerosis in the chick.

EXPERIMENTAL ATHEROMATOSIS AND ATHERO-HEPATOSIS IN DUCKS AND GEESE; ITS REVERSIBILITY AND ITS CLINICAL IMPLICATIONS

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Studies of the spontaneous occurrence of atheromatosis and atherohepatosis in wild ducks revealed the percentage to be extremely small as compared with domesticated Peking ducks, Muscovy ducks, and geese. Because of the ease of handling and feeding, the common goose was chosen for more extensive investigation. Atheromatosis and atherohepatosis were produced in forced-fed geese. A series of experiments are described showing the reversibility of this process by the use of diet, exercise, and pancreatic extract.

Pathologically the lesions produced in geese resemble atheromatosis in the human being, the most common variety of so-called "arteriosclerosis." The reversibility of the pathologic process adds further evidence to the rational use of diet, exercise, and, in selected cases, pancreatic extract in the treatment of atheromatosis and its many complications irrespective of the anatomic site of the vascular lesion.

Motion pictures of experimental work will be shown.

SIMULTANEOUS STUDIES ON THE SERUM LIPIDS AND THE ELECTROPHORETIC PATTERN OF THE SERUM PROTEIN IN MAN: (1) ACTION OF INOSITOL AND OTHER SUBSTANCES

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This project was concerned with the action of various substances such as choline, glucuronic acid, and pyridoxine, but chiefly with the action of inositol. A group of patients was selected who had clinical evidence of some disorder of lipid metabolism as indicated by clinical findings and confirmed by blood chemistry. The total lipids, fatty acids, lipid phosphorous, and cholesterol, were determined on the sera of these patients, and, simultaneously, electrophoretic patterns were determined before and after ether extraction. Inositol, 1.0 Gm. three times a day, was administered, without any attempt to control the diet and without other medications unless so noted. A decrease in total lipids and fatty acids with an increase in the lipid phosphorous and cholesterol was constantly produced in the earlier phases of treatment. As the period of treatment continued, there was a drop in the lipid phosphorous level and in the cholesterol. The only side reactions to the inositol are headache and gastrointestinal upset or diarrhea, which occurred in only a small percentage of cases. Since the production of a marked decrease in all lipids was accomplished by the use of inositol without diet, it is felt that the substance is a potential weapon against one of the probable factors in atherosclerosis.

THE VASCULAR PROBLEM IN DIABETES MELLITUS

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Present-day opinion stresses that the peripheral vascular lesions which occur in diabetic patients are indistinguishable pathologically from the arteriosclerotic changes which develop in nondiabetic subjects. The validity of this opinion was analyzed in a series of forty-eight diabetic patients ranging from 6 to 45 years in age. On the basis of accepted criteria (roentgenography, oscillometry, and vasomotor index), none of this group presented evidence of peripheral arteriosclerosis. An evaluation of the circulation by the microplethysmographic method following autonomic blockade with tetraethylammonium disclosed the unsuspected existence of structural vascular disease in twelve of these forty-eight patients. This was manifested by a decrease in the amplitude of the volume pulsations and a decrease in the rate of peripheral blood flow. The association of a normal oscillometric index and an abnormal microplethysmogram suggests that the fundamental peripheral vascular lesion in diabetes mellitus is a specific angiopathic alteration of the smaller blood vessels analogous, perhaps, to the vascular changes found in diabetic retinopathy or in the nodular variety of intercapillary glomerulosclerosis. The evidence implies that the primary mechanism responsible for the development of premature arteriosclerosis in diabetes may be related to mechanical rather than to metabolic factors.

In an attempt to elucidate the pathogenesis of the minute vascular changes, the plethysmograms have been correlated with various aspects of the diabetic state, namely, the level of the blood cholesterol, the insulin requirements, the presence of retinal and renal changes, and the severity and duration of the diabetes.

These investigations suggest that concepts previously entertained regarding the occurrence of vascular lesions in diabetes mellitus necessitate re-evaluation. Based upon this study, an analysis of the vascular problem in diabetes from the therapeutic and developmental standpoints will be presented in detail.

CHANGES IN THE CUTANEOUS ARTERIOLES IN THE ARM AND LEG IN COARCTATION OF THE AORTA

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Specimens of skin and subcutaneous tissue were excised for biopsy from the upper arm and calf of nine ambulatory patients who had coarctation of the aorta. The tissue was fixed in formaldehyde U. S. P. (1:10), blocked in paraffin, and stained with hematoxylin and eosin, elastin H, Van Gieson, and elastin-Van Gieson stain. To determine the degree of thickening of the arteriolar wall and the alteration in the wall-to-lumen ratio, measurements were made according to the method described by Kernohan, Anderson, and Keith. The first four arterioles in each slide were measured as the slide was moved from left to right. Most of the arterioles measured were located in the deeper portion of the cutis.

Thickening of the arteriolar wall and a decrease in the wall-to-lumen ratio as compared to normal were the characteristic findings in all cases. Study of each arteriole revealed structural changes consisting of endothelial hyperplasia, proliferation and thickening of the inner elastic lamina, hyperplasia of nuclear elements in the media, and apparent reduction in the size of the lumen. Not

all arterioles were equally affected, although most of the arterioles studied showed some changes from the so-called normal. The changes were similar to those previously observed in a study of the cutaneous arterioles of a group of patients who had essential hypertension. In the sections taken from the leg in this group of patients with coarctation the changes in the cutaneous arterioles were of the same degree as those taken from the arm.

DOES ARTERIOSCLEROSIS DEVELOP BY EPISODIC STAGES?

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There is no doubt that the incidence of arteriosclerosis increases with age, but this does not necessarily mean that the effects of age are causative, for other "scars" also accumulate with each successive decade. On the clinical side, it is generally recognized that many forms of human arterial lesions develop by episodic stages. On the experimental side, "crops" of arterial lesions can be produced in a matter of days, more or less at will, by a variety of procedures in several species of animals. Moreover, in the majority of cases these experimental procedures are as applicable to young as to old animals. In the light of these clinical and experimental observations it has seemed proper to inquire: Do the lesions dumped in the "wastebasket of arteriosclerosis" develop in a similar manner?

Recently the authors have started a systematic review of human arterial lesions with this question in the foreground. The meager data accumulated to date have confirmed previous observations. It is easy to find uniform early lesions whose clinical and anatomic features suggest development in episodic fashion in a matter of days. Further, it is not difficult to find cases with two or more "crops" of lesions; and, even in advanced arteriosclerosis, it is possible to pick out lesions of recent vintage. Some of these lesions will be presented.

From the studies thus far made it would appear that in all forms of arterial lesions, both human and experimental, there is good evidence for their development by episodic stages, and the tempo of the episodes is more in keeping with days than it is with decades.

THE USE OF RADIOACTIVE SODIUM IN THE DIAGNOSIS OF PERIPHERAL CIRCULATION IN PERIPHERAL ARTERIOSCLEROSIS

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Radioactive sodium, following its injection into the antecubital vein, can be followed throughout the body with a Geiger counter. The material is administered in amounts of 100 microcuries in 5.0 c.c. of distilled water. The half-life of radioactive sodium being 14.8 hours, the total exposure of tissue to gamma rays is less than 1 roentgen. The method has been employed in 2,000 cases without harm to patients or to those handling the material.

The time between injection and the demonstration of the arrival of radioactive sodium at any point in the body measures the circulation time between the points involved and has varied depending upon the degree of arterial occlusion.

Radioactive sodium leaves the plasma and eventually comes into equilibrium with the extracellular sodium in the body. The rate of this build-up has been determined in patients with and without arteriosclerotic peripheral vascular disease. In the presence of such disease the rate of transfer of the radioactive sodium from plasma to extracellular fluid has been found to vary from the normal.

The degree of variation has provided accurate clinical indications of the degree of occlusion of main and collateral channels, and, when charted in individual cases, has given more accurate information regarding the condition of main and collateral vessels than other tests in the same patients. It has also indicated prognosis, the effects of treatment, the probable benefit of surgery, and the type of surgery which local parts will tolerate.

THE PROGNOSIS IN ABDOMINAL AORTIC ANEURYSM

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Data were compiled from the records of 101 cases of abdominal aortic aneurysm, almost all of which were due to arteriosclerosis. These records were selected only when there was unequivocal evidence of aneurysm, and cases of true dissecting aneurysm were not included. Eighty-five per cent of the patients have been traced. From the present data it has been determined that 65 per cent of patients survived one year or longer after the date of the original diagnosis at the Mayo Clinic. Fifty per cent survived three years or longer, and 20 per cent five years or longer. These figures are approximate and may be altered by information subsequently obtained. However, it is not believed that they will be materially changed.

NATURE OF THE HYALINE MATERIAL IN ARTERIOLO-SCLEROSIS OF KIDNEY

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The hyaline material appearing with arteriosclerosis of the kidney is being studied by a variety of methods to attempt to determine its nature, or at least to compare it with the fatty and other components of larger arteries showing intimal atherosclerosis.

Extractability of the hyaline material varies, depending on whether the tissue is unfixed or fixed. For example, all of the material potentially stainable with Sudan black or Sudan III (which stain neutral fats) was removed in five minutes from the arterioles of unfixed kidney by treatment of frozen sections with acetone, and largely removed in one minute; while this same material, formalin-fixed, was not completely removed from frozen sections even after twenty-four hours of treatment by acetone. Using other methods, there was no difference between fresh and unfixed tissue. Finally, some of the methods required unfixed tissues.

The Sudan black and Sudan III stains indicate that the hyaline of the arterioles contains neutral fat, as do the plaques of intimal arteriosclerosis.

Application of a method for fatty acids (Fischer's method and Gömöri's method) indicated the presence of fatty acids in unfixed tissue. However, it is possible that hydrolysis had occurred during the post-mortem period or during refrigeration. The fatty acids in the hyaline arterioles are nearly all saturated, though a little unsaturated fatty acid is present (osmic acid stain), while in the atherosclerotic plaques of the aorta there were unsaturated fatty acids at the periphery of the plaques. Hyaline arterioles do not give positive staining for lipase, using Gömöri's method, while sections of liver prepared at the same time give a strong positive reaction.

Calcium was not identified in the hyaline arterioles of the kidney, using the Von Kossa method, but could be demonstrated in many of the plaques of the sclerotic aorta.

The hyaline material does not give the staining reactions of amyloid.

The periodic acid method colors the hyaline present in arteriosclerotic lesions, indicating the presence of carbohydrate (McManus, J.F.A.: *Stain Technology*, 23:99, No. 3, 1948).

THE PRINCIPAL SYNDROMES ASSOCIATED WITH CEREBRAL ARTERIOSCLEROSIS

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In an effort to clarify the clinical picture of arteriosclerosis in the light of present-day knowledge, the various symptom complexes produced by diffuse and local involvement of the brain are presented. Each is discussed from the standpoint of the latent asymptomatic period, the period of functional insufficiency (partial occlusion or narrowing), and the period of functional failure (total occlusion). The effects of injury and of constitutional conditions, such as anemia and heart failure, are also emphasized with particular reference to the concept of cerebral circulatory compensation.

Among the syndromes that have been well established by the clinical and pathologic studies of many workers may be mentioned those affecting the anterior, middle, and posterior cerebral arteries, the superior cerebellar, the anterior inferior and posterior inferior cerebellar arteries, the vessels making up the circle of Willis, and the pressure changes caused by arteriosclerotic aneurysms. The relation of cerebral arteriosclerotic changes to the Parkinson syndrome and certain psychoses is also reviewed. The pseudoemotionalism seen after repeated cerebral accidents and the problem of cerebral vasospasm are discussed.

In conclusion, the favorable prognosis in some of these conditions and the good response to rehabilitation therapy is described in a few brief case reports.

RESULTS OF TREATMENT OF CORONARY ARTERIOSCLEROSIS WITH CHOLINE

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A series of 115 patients with proved coronary thrombosis and myocardial infarction were treated with choline after recovery from the acute attack and discharge from the hospital. These patients were divided into three groups: (1) Fifty-two patients given choline for one year, (2) a group of thirty-five given choline for two years, and (3) a group of twenty-eight patients given choline for three years. The dosage of choline varied from 6 to 32 Gm. daily. These series of patients were compared with a group of "alternate controls" consisting of 115 patients with proved coronary thrombosis and myocardial infarction who were discharged from the hospital under identical conditions. The patients in this series were observed over the same period of time and did not receive choline.

The detailed analyses of each choline-treated group as compared with its "control" series revealed that the subsequent mortality rate of patients was significantly reduced under choline treatment. The causes of death from recurrent coronary thrombosis and from cardiac congestive failure and the possible action of choline as a lipotropic agent in coronary arteriosclerosis are discussed.

These studies suggest that the lipotropic agent, choline, is of value in the treatment of coronary arteriosclerosis and merits further trial and observation in this disease.

FAT ABSORPTION AND ATHEROSCLEROSIS. A THEORY ON THE DEVELOPMENT OF ATHEROSCLEROSIS WITH AGEING

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In studies on the fundamental aspects of fat absorption we have observed conditions which may have a profound effect on the formation of atherosclerosis.

After ingestion of small quantities of fat, the chylomicron curves of twenty-five young and thirty older persons (average ages 18 and 76 years) showed a fundamental difference. In the young group, the count reached a maximum within two to three hours and returned to fasting levels at the fifth hour. In the older group, the counts rose continuously until the end of the twelfth hour and did not return to fasting levels until twenty-four hours had elapsed. These differences between old and young normal subjects developed gradually with age, and reached their maximum at an age of 50 years. The total number of chylomicrons was consistently and considerably higher in the older group. That the difference between the two groups was not due to disposition of fat by the body was shown by intravenous fat tolerance curves, which were similar for both young and old. Further tests have shown that older subjects on normal diets have a constant hyperchylomicronemia. This can be reduced to the level of young persons by the use of lipase preparations or detergents.

Chylomicrons are macromolecular bodies containing largely neutral fats but also cholesterol. Hueper, Moreton, and others have shown that macromolecular bodies can be deposited and can damage the internal layers of arteries. The neutral fats seem to disappear rapidly from the intima and subintima, while the cholesterol accumulates gradually, giving rise to the degenerative processes of atherosclerosis.

Our results on diminished digestive secretions, digestion, and absorption in older persons will be discussed in an attempt to explain the observed phenomena.

THE EFFECT OF ESTROGENS UPON THE PARTITION OF THE SERUM LIPIDS IN FEMALE PATIENTS

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Fasting total serum lipids, lipid phosphorus, and total cholesterol have been determined repeatedly on eleven female patients receiving estrogens for various reasons. The study included thirty control values when the patients were not receiving estrogens and forty-six determinations made during periods of estrogen administration. The group comprised one patient with still regular menses, three patients who had had normal climacterics, one patient who had had an artificial menopause by irradiation, and six patients who had had some form of surgical menopause. Periods of observation ranged from two weeks to twenty-six months. In several instances there were two or more control periods alternating with two or more periods of estrogen administration.

Eight patients received oral Estinyl in doses of 0.02 to 0.10 mg. per day, one received oral Stilbesterol in doses of 0.5 to 1.0 mg. per day, and two received 10,000 to 30,000 units of Progynon subcutaneously daily.

In all cases there was a sharp reduction in the ratio of total cholesterol to lipid phosphorus during periods of estrogen administration. This change was usually effected by an elevation of serum lipid phosphorus and a fall in total cholesterol; however, in one instance the average total cholesterol level was

unchanged, and in one it actually increased. In only one patient was the lipid phosphorus during periods of estrogen administration lower than the control values, but this was accompanied by a decrease in cholesterol sufficient to bring about some decrease in the cholesterol-lipid phosphorus ratio.

The possible relationship of the effect of estrogens upon the serum lipids to the lower incidence of arteriosclerosis in women, particularly before the climacteric, is suggested.

HISTOLOGY OF INFARCTED HEART MUSCLE

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Few authorities describe extensive regeneration of damaged skeletal muscle in adult mammals, the general opinion being that regeneration, if it occurs at all, is abortive. The regular enlargement and proliferation of muscle nuclei is considered by some as an indication of regeneration, by others as purposeless, "atrophic nuclear proliferation." I believe that the nuclear enlargement and subsequent nuclear amitotic division is due to a decompression resulting from the wasting of sarcoplasm. Observations on curarized and tetanized skeletal muscle confirmed this view (Altschul, R.: *Arch. Path.* 47:223, 1949). In studying infarcted human heart muscle, I found that inside or in the vicinity of the scar tissue, nuclei of damaged muscle fibers are enlarged, sometimes nearly to the width of the single muscle fiber, but nuclear proliferation is very rare. Surprisingly, the muscle fibers are not markedly thinned. The nuclear enlargement may be caused by the same mechanism which leads to the formation of "muscle giant cells" or "nuclear tubes" in skeletal muscle, namely, the loss of pressure equilibrium between nucleus and sarcoplasm, with ensuing changes in osmotic pressure and imbibition of the nucleus. Although the moderate decrease in width of the heart muscle fibers does not conform with such an explanation, it may be that hypotonia of the damaged fibers is responsible for the nuclear expansion. It remains to be seen why the nuclei fail to divide after reaching the "critical phase" or why the latter is farther from the norm than in skeletal muscle. Comparing damaged cardiac with damaged skeletal muscle, it is concluded that the attempt at regeneration in the heart is less than in skeletal muscle or, contrarily, that by the steady contraction ("self massage") of heart muscle, the thinning of fibers and the "atrophic nuclear proliferation" are completely or partly prevented.

THYROID ACTIVITY AND TISSUE CHOLESTEROL DISTRIBUTION

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In a preliminary experiment, rats were fed cholesterol and bile salt, one group receiving in addition thyroid USP, and another group, thiouracil with the diet. Chemical determinations of plasma cholesterol levels indicated the expected changes, namely, low values for the hyperthyroid group (average, 39 mg. per cent) and high values for the thiouracil-fed animals (average, 251 mg. per cent). The cholesterol content of the liver, however, did not reflect cholesterol content of the plasma, but was very similar in these two groups (average values, 1.6 per cent and 1.5 per cent cholesterol, respectively). Histologic examination of the aorta revealed a slight cholesterol deposition in both experimental groups. In spite of the very low plasma cholesterol of the thyroid-fed rats, isolated small crystals were seen in most animals of this group, scattered through the endothelium of the aorta; otherwise, the structure of the aorta was normal. In the thiouracil-fed

group, the aorta had an entirely different aspect, showing a slight tendency to thickening of the intima associated with small localized cholesterol deposits. As far as could be estimated, not more, but, if anything less, cholesterol was deposited in the aorta of these hypothyroid rats, although the plasma cholesterol concentration in this group was appreciably higher.

Thus, neither the liver cholesterol content nor the deposition of cholesterol in the aorta appeared to depend upon the plasma cholesterol level. This might indicate that other factors play a role in the mechanism responsible for cholesterol deposition.

THE HAMSTER AS EXPERIMENTAL ANIMAL FOR THE STUDY OF ATHEROMATOSIS

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Sixty hamsters were fed 50 mg. of cholesterol powder (Armour) in gelatine capsules daily for from 30 to 130 days and thirty were fed a control diet without cholesterol. Several batches of hamsters of the same sex (male), age (3 months), and weight (90 to 100 grams) obtained from the same hamstery differed as to normal blood cholesterol values. One series had an average of 66 mg. of cholesterol per 100 ml. of blood and two other series had 142 mg. and 143 mg., respectively. Within each group of animals, the blood cholesterol values were fairly uniform. All three series of hamsters had an average liver weight of 2.36 grams and 600 mg. cholesterol per 100 grams of wet liver weight. There was, however, considerable variation in liver weight and liver cholesterol within each group of animals. In hamsters with low initial blood cholesterol values, both the blood and the liver cholesterol doubled after thirty days of feeding. In hamsters with a normally high blood cholesterol, the same effect was obtained, but only after sixty days of feeding. Upon further cholesterol feeding, the blood cholesterol level did not increase substantially, but after 130 days of feeding, the liver cholesterol was four times the original level. All cholesterol-fed hamsters had increased liver weight and liver steatosis reflecting the results of chemical analysis of that organ. Steatosis of suprarenal glands exceeded that of the liver. Parallel to the degree of steatosis, testicular atrophy was observed. Isolated subintimal foam cells were seen in the ascending aorta of but 10 per cent of cholesterol-fed hamsters. Some of these animals had marked, and others moderate, elevation of total blood cholesterol. None of the hamsters showed any appreciable degree of atheromatosis.

The golden Syrian hamster, therefore, seems ill suited for production of atheromatosis by feeding of cholesterol.

A METHOD FOR THE ESTIMATION OF 7-KETOCHOLESTEROL IN SERUM

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In the course of a study on the effect of possible cholesterol metabolites on the development of arteriosclerosis, a quantitative method for the determination of 7-ketocholesterol has been developed. Although this compound was not included in the list of oxidized sterols isolated by Ruzicka from arteriosclerotic lesions of human aortas, its presence there was indicated by the finding of $\Delta 3,5$, cholestadiene-7-one, a substance formed when 7-ketocholesterol is treated with hot alkali.

The serum lipids are extracted with alcohol-ether. The fats are saponified in this extract with potassium hydroxide at room temperature in the presence of cyanide to minimize auto-oxidation and the nonsaponifiable lipid fraction is isolated. The oxidized sterol fraction is separated from the bulk of the cholesterol by the countercurrent distribution technique. The sterols are precipitated from alcoholic solution with digitonin; the precipitate is washed with alcohol and ether and then dissociated with pyridine. The digitonin is precipitated from the pyridine solution with ether. The ether solution containing the sterols is washed free from pyridine with dilute hydrochloric acid. The amount of 7-ketocholesterol present is estimated by measuring the optical density of the residue dissolved in absolute alcohol. Good recoveries are obtained when known amounts of 7-ketocholesterol are added to serum.

Application of this procedure to the sera of dogs with arteriosclerosis proved at autopsy shows the presence of a small amount of material precipitable with digitonin which has distribution coefficients and an ultraviolet absorption curve identical with those given by 7-ketocholesterol. In addition, upon treatment with hot alcoholic potassium hydroxide this material is converted into a substance having the ultraviolet absorption curve of Δ 3,5, cholestadiene-7-one which is formed when 7-ketocholesterol is treated in a similar way. These properties identify 7-ketocholesterol with a considerable degree of certainty.

A STUDY OF ATHEROSCLEROSIS IN DIABETES MELLITUS

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This paper is a report on eighty-nine unselected diabetic patients from Mt. Sinai Hospital of Cleveland in whom an attempt has been made to show the presence of atherosclerosis. Five diagnostic procedures were found to be of especial value: the carotid sinus pressure test, palpation of supraclavicular pulsations, the presence of calcification of the abdominal aorta as shown by roentgen study, the determination of occlusive arterial changes in the legs, and the presence of calcification in the aortic arch in chest films. The percentages of these diagnostic signs found in diabetic patients are evaluated and tabulated.

GLOMERULAR OBSOLESCENCE IN ARTERIOSCLEROSIS; IDENTITY AND SIGNIFICANCE

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With the periodic acid-Schiff reagent method it can be shown that arteriosclerosis, pyelonephritis, and glomerulonephritis alter the renal glomerulus in specific fashions. The recognition of the patterns of obsolescence which differ in these conditions allows the evaluation of the part played by each process in cases of renal disease. It does not explain the associated hypertension.

Arteriosclerosis produces knots of wrinkled basement membrane upon which hyaline has been deposited. The capsular space is filled in by another hyaline material. In the one scar, various stages of glomerular obsolescence are seen.

On the other hand, pyelonephritis involves the glomeruli by invasive inflammation, producing degrees of fibrosis of the tuft. Again, unlike arteriosclerosis, glomerulonephritis involves chiefly the glomerular capillaries, but epithelial crescents are formed after one week. Tubule-like organization occurs in the crescent. These "tubules" may persist beyond the obliteration of the glomerulus.

The changes in the glomerular basement membrane in arteriosclerosis can be interpreted as progressing in two phases. The original wrinkling might be the effect of ischemia as MacGregor suggested. The hyaline deposit could be derived from the circulating blood coursing at reduced speed through the ischemic glomerulus.

The arteriosclerotic or ischemic glomerulus is important from two aspects. In the first instance, fewer cases of "essential" hypertension would be so classified if the lesion were recognized. Second, observation of the developing glomerular lesion may provide clues as to the basis of the loss of kidney tissue in cases of arteriosclerosis.

AGEING AS A FACTOR IN THE RENAL HEMODYNAMIC RESPONSE TO A STANDARDIZED PYROGEN TEST

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Changes in glomerular filtration rate (GFR), effective renal plasma flow (RPF), and filtration fraction (FF) were evaluated following the intravenous administration of 50 million killed typhoid organisms in fifty-one men between the ages of 20 and 89 years. All subjects were normotensive and free from demonstrable cardiovascular or renal disease. The constant infusion technique was used for determining inulin and PAH clearances. Eleven twenty-minute urine collection periods were obtained following the administration of the pyrogen in three age groups: 20 to 49 years, 50 to 69 years, and 70 to 89 years.

The results obtained were as follows: No significant changes in the mean GFR were observed in any of the age groups following administration of the pyrogen. A marked increase was noted in the RPF of 363 c.c. (63 per cent of base line) in the 20 to 49 year age group; 349 c.c. (80 per cent) in the 50 to 69 year age group, and 223 c.c. (81 per cent) in the 70 to 89 year age group. The mean FF decreased from 19.7 to 12.1 (−38.6 per cent of base line) in the 20 to 49 year age group, from 21.0 to 12.7 (−39.3 per cent) in the 50 to 69 year age group, and from 23.4 to 12.7 (−45.7 per cent) in the 70 to 89 year age group.

Although it is known that the incidence and degree of renal arteriosclerosis and the mean FF increase with increasing age and the GFR and RPF are decreased in the aged population, it must be concluded from these observations that under the conditions of this study the renal arterioles of the aged individual can dilate as effectively as those of the young individual.

THE SILICA CONTENT OF THE AORTIC WALL IN ARTERIOSCLEROSIS

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A study was made of the silica content (SiO_2) of thirty-five samples of the thoracic aorta from individuals between the ages of 6 months and 96 years. For evaluation of the degree of arteriosclerosis, estimations were also made of the total ash, calcium, total lipid, and cholesterol content of the tissue. The adventitia was removed before analysis. Homogenization of the samples was obtained by treating the tissue with liquid air and subsequent grinding in a metal grinder. The silica determinations were performed by a modification of King's method.

The average silica content of the aortic wall was 14.0 mg. per cent and showed no definite change with age, whereas a marked rise was observed in the total ash, calcium, and cholesterol content with advancing years. The coefficients of correlation between total ash, calcium, total lipid, cholesterol, and silica were $+0.15$, $+0.23$, -0.10 , and -0.13 , respectively.

METABOLIC STUDIES IN CORONARY THROMBOSIS

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A series of studies was conducted on a group of fifty patients with recent coronary thrombosis and on a group of "control" patients, and normal individuals. These consisted of simultaneous determinations of (1) blood serum cholesterol, cholesterol esters, cholesterases, phospholipids, and total lipids; (2) serum albumin and globulin; (3) cephalin flocculation and thymol turbidity reactions for the beta and gamma globulins; and (4) blood iodine levels. All these determinations were carried out from one to three times in the same patients and comparative analyses were made of disturbances of blood plasma and serum lipid and lipid-protein relationships.

Abnormal, high elevations in the total blood serum lipids, the phospholipids, and the blood serum cholesterol levels are described and their clinical significance is discussed. A consistent disorder in the lipid enzyme cholesterol esterase is analyzed and its clinical bearing in the patients with coronary thrombosis is discussed.

Instability of the blood serum and plasma lipids is described, as well as that of the beta and gamma globulins, in recent cases of coronary thrombosis.

The blood iodine levels are reported and their relationship to the blood serum cholesterol, lipid, and protein fractions is mentioned.

FAT TOLERANCE TESTS IN CORONARY THROMBOSIS

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A physiologic fatty meal consisting of a breakfast of eggs, bacon, bread and butter, coffee, and cream was administered as a "fat tolerance test" to a series of twenty-five patients with recent coronary thrombosis. The results were compared with those of a similar "fat tolerance test" performed on a series of normal individuals and on a series of patients suffering from miscellaneous diseases. Blood serum determinations were made of cholesterol, cholesterol esters, cholesterol enzyme esterases, phospholipids, and total lipids in the fasting patients, and hourly for four hours following the "fat tolerance" meal.

This investigation revealed that patients with recent coronary thrombosis have an abnormally high rise in the blood serum lipid constituents following the ingestion of a fat-test meal. Attempts are described to alter alimentary hyperlipemia by the use of fat dispersal or wetting agents as well as the use of lipotropic agents.

Simultaneous studies were carried out of chylomicron determinations in this series and the abnormal rises in chylomicron counts following fat tolerance tests are discussed in relationship to the behavior of the various lipid constituents discussed.

THE SIGNIFICANCE OF BLOOD SERUM CHOLESTEROL INSTABILITY IN CORONARY ARTERIOSCLEROSIS

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A. Thirty normal "control" subjects were tested on two or more occasions for the blood serum cholesterol content; this value was found to vary less than 10 per cent for periods up to one year.

B. Thirty patients suffering from miscellaneous diseases were tested for serum cholesterol under the same conditions; these cholesterol values were found to be subject to wide fluctuations.

C. Fifty patients who had recent coronary thrombosis were tested under the same conditions for periods up to one year; these patients with coronary arteriosclerosis were uniformly found to display wide variations in blood serum cholesterol content over periods up to one year.

D. Fifty patients with recent coronary thrombosis were treated with choline under the same conditions as the patients in (C) and studied for periods up to one year. Serum cholesterol determinations were made before, during, and after treatment with choline, and revealed uniformly wide and inconstant variations in cholesterol values. As many patients revealed increases as decreases in cholesterol values.

E. When determined by a reliable method, variation in blood serum cholesterol in an individual suggests the presence of a disease and/or some metabolic disorder.

F. Variations in serum cholesterol appeared to be directly related to the activity of cardiac lesions, with particular reference to coronary insufficiency and congestive failure. In these two latter states the instability of cholesterol was markedly increased when compared with that encountered in a group of patients who had experienced a coronary thrombosis three or more years ago and who were subsequently symptom free.

THE EFFECT OF CRUDE RENAL EXTRACTS AND PURIFIED RENIN ON VASCULAR LESIONS IN EXPERIMENTAL MALIGNANT RENAL HYPERTENSION

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Crude hog renal and liver extracts and purified hog renin were injected prophylactically into dogs subjected to simultaneous bilateral renal artery constriction previously found to produce consistent experimental malignant hypertension. Injections were made daily and intramuscularly for three months prior to and during survival or up to one month subsequent to renal artery constriction. Crude hog renal cortex extract containing renin was highly effective in protecting against the hypertension, at least partially effective against the arteriolonecrotic lesions, and partially effective in prolonging survival time (four dogs). Purified

hog renin was only partially effective in protecting against the hypertension and the arteriolonecrotic lesions and in prolonging survival time (four dogs). Crude hog whole kidney extract containing renin did not have an antihypertensive effect, and was only partially effective in protecting against the arteriolonecrotic lesions and in prolonging survival time (four dogs). Crude hog liver extract had no antihypertensive effect and was doubtfully effective in protecting against the arteriolonecrotic lesions of malignant hypertension and in prolonging survival time (three dogs). The mechanism of the antihypertensive effect is not yet determined. Antirenin may be involved. The mechanisms of the protection against arteriolonecrotic lesions and the prolongation of survival time remain to be determined. Present evidence suggests the possibility that the arteriolonecrotic lesions may be due to a renal necrotizing substance which is not renin. (A method which will produce consistent experimental malignant hypertension in the dog has been devised.)

FAT TOLERANCE CURVES IN RAT AND RABBIT USING I¹³¹

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Iodinated cottonseed oil was given to both species by stomach tube in a dose of 7 c.c. per kilogram (0.1 c.c. of the oil yielded 8,000 counts per minute). Samples of blood were taken at regular intervals and blood fat was measured in terms of radioactivity.

The results showed a distinct difference between the two species. In both, the peak concentration was reached at approximately the same time (fifteen hours); in rats the rate of decay was rapid, reaching the initial concentration at forty hours, while in rabbits, hyperlipemia persisted for more than sixty hours. This difference in fat metabolism may be related to the production of experimental atheromatosis in rabbits and the inability to induce it in rats.

THE EFFECT OF GRADED DOSAGES OF IODIDE ON PLASMA AND LIVER CHOLESTEROL OF NORMAL, CHOLESTEROL-FED AND THYROIDECTOMIZED RABBITS

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Groups of rabbits (normal animals, normal animals fed cholesterol, normal animals fed iodide, and normal animals fed cholesterol and various dosages of iodide) were compared with similar groups of thyroidectomized rabbits. Cholesterol dosage was 400 mg. daily and iodide dosages 1, 5, 10, 20, and 40 mg. daily in normal animals and cholesterol-fed groups and 1 and 40 mg. daily in thyroidectomized and thyroidectomized, cholesterol-fed groups.

Normal rabbits and iodide-fed normal rabbits showed little change in plasma cholesterol. The concentrations were episodically increased by cholesterol feeding. Plasma cholesterol levels were further increased by iodide (1 mg. daily) during cholesterol feeding; larger dosages of iodide depressed the hypercholesterolemia. The greatest increase in plasma cholesterol was elicited by thyroidectomy with cholesterol feeding. In thyroidectomized, cholesterol-fed animals,

both 1 and 40 mg. iodide dosages depressed plasma cholesterol, the larger dosage having the greater effect. Thyroidectomy alone, with or without iodide, elicited a transient hypercholesterolemia.

Cholesterol feeding doubled hepatic total cholesterol in normal animals; this change was not affected by iodide, but was somewhat depressed by thyroidectomy. The proportion of hepatic ester cholesterol was doubled in cholesterol-fed normal animals. The increase in ester fraction was exaggerated by dosage with 1 mg. iodide; this effect disappeared with further increments of iodide dosage which tended to restore the proportion toward normal. Thyroidectomy alone, as well as iodide alone, decreased hepatic ester cholesterol fractions.

In conclusion, the effect of iodide on plasma cholesterol is variable and dependent on dosage in normal animals fed cholesterol, but wholly depressing in thyroidectomized, cholesterol-fed animals. The iodide has a similar action on the hepatic ester formation. Changes in hepatic ester cholesterol fraction tend to be concurrent with changes in total plasma cholesterol. The effect of iodide does not depend on the presence of the thyroid gland.

American Heart Journal

VOL. 38

OCTOBER, 1949

No. 4

Original Communications

ARTERIAL AIR EMBOLISM

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ACCIDENTS due to air embolism may be divided into two types, depending on the site of entrance of the air into the body. The distinction between these types is vital, since there is a tremendous difference in the symptomatology and in the amount of air necessary to produce serious manifestations or death. The first type is that in which the air enters a systemic vein and tends, if present in sufficient quantity, to result in obstruction of the right ventricular outflow tract. Amounts of air up to 100 to 150 c.c., or more, may be necessary to produce death, although the result is determined by a number of factors, such as the pressure of the injected gas, the speed of the injection, and the position of the patient at the time the air enters the circulation. This type of embolism may occur as an accident under a number of different circumstances in medical practice, and there has been no field of medical endeavor free from its occurrence. It has been called *pulmonary air embolism*, since it is the pulmonary circulation which is involved in the obstructive manifestations. We have considered this type of embolism in a previous communication,¹ to which the reader is referred for further details. The present report will limit its considerations to the second type.

Air which gains entrance to the pulmonary veins produces an entirely different clinical picture, and presents many features which do not correspond to those presented by the previous type. It has been called *arterial air embolism* since its serious manifestations are dependent upon obstruction of systemic arteries, especially of the central nervous system and coronary vessels. This type, as would be expected, has been a menace in procedures dealing with the thorax, such as pneumothorax, thoracentesis, and various thoracic surgical procedures.

HISTORICAL SUMMARY

In 1912 Brandes² accidentally demonstrated the mechanism of arterial air embolism when he attempted to outline the extent of an empyema cavity by means of an injection of bismuth paste through a thoracic sinus. The patient

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Supported by RG 194-C, United States Public Health Service.

developed a generalized convulsion with conjugate deviation of the eyes, and death occurred in twenty-four hours. Post-mortem examination revealed bismuth in the smaller blood vessels of the cerebral cortex on both sides, as well as in other systemic arteries. Serial sections made from the walls of the sinus used for the injection revealed bismuth as far as the pulmonary capillaries and veins. Here the rubber catheter used to inject the bismuth had evidently produced a mechanical injury of such a nature as to open some of the small veins. The symptoms in this case were identical with those which had been attributed by chest specialists to "pleural shock" or "pleural eclampsia" in cases of pneumothorax. It was demonstrated, therefore, that substances injected into the pulmonary veins could readily reach the cerebral circulation and produce disastrous results, and the question was then raised as to the possibility that gases could follow a similar route and be as disastrous in their effects, thus accounting for localized neurological manifestations not explained by the pleural shock theory. As early as 1913 Brauer³ reported his strong conviction that all serious accidents of the type referred to as pleural shock were in reality due to air embolism. In support of this contention, Gunderman⁴ in 1921 injected air into the pulmonary veins of animals and observed it entering immediately into the coronary arteries and riding there without a tendency to pass on through the capillary bed.

Despite this evidence, many students of the problem continued to hold to the pleural shock theory of origin for pneumothorax accidents,⁵⁻⁸ and Vandriessche⁹ went so far as to state that "the theory of gas embolism should be abandoned." As far back as 1907 Capps and Lewis¹⁰ had presented strong experimental evidence to indicate that irritation of the *inflamed* visceral pleura by various means could result in blood pressure-lowering reflexes. In 1937 Capps¹¹ presented a summary of the evidence for pleural shock and against air embolism. He pointed out that stimulation of the normal pleura of an animal results in no response, but, when an acute pleurisy has been produced previously, stimulation results in manifestations which may be of two types. The first is that of vagal irritation, as shown by slowing of the pulse, or even by heart stoppage. Fainting may result, but recovery is prompt, there is no danger involved, and the reaction may be abolished by the giving of atropine. The second involves a different (vasomotor) type of reflex. It is manifested not by cardiac irregularity but by tachycardia, with a rapidly falling blood pressure, the appearance of shock, and the possibility of death. The upright posture is apparently conducive to this type of reaction, and Capps blamed the sudden deaths in pneumothorax and thoracentesis work on this vasomotor type of reaction. He had further strengthened his argument by purposely stimulating the visceral pleura of human subjects during the tapping of pleural effusions, and had demonstrated a drop in the blood pressure.

As objections to the air embolism theory he further pointed out that: (1) syncopal phenomena are not encountered often enough in procedures that involve the injection of air, that is, pneumothorax; (2) syncope occurs most often in simple exploratory puncture wherein no air is injected; and (3) numerous individuals who have succumbed to pleural shock have shown no evidence at post-mortem examination of air emboli in the brain or coronary arteries.

Though these arguments *for* the existence of pleural shock have been strong, the arguments *against* the possibility of air embolism have not been convincing, and as time has passed more and more evidence has become available to refute them. Certainly the neurological manifestations which represent focal lesions in the central nervous system are common in pneumothorax and thoracentesis accidents, and these are very difficult to explain on the basis of a shock mechanism, especially in younger individuals without pre-existing cerebral vascular disease. Air embolism, on the other hand, provides a very satisfactory explanation. Furthermore, many cases have been reported in which air has been seen in the retinal vessels of patients suffering from attacks of the type under consideration.¹²⁻¹⁶ In one instance air has even been demonstrated roentgenologically in the cerebral vessels.¹⁷

It is true, as Capps¹¹ has stated, that in some cases supposed to be arterial air embolism no air is found on post-mortem examination, but this is true mainly of those cases in which death is delayed, and in these the pathological lesions found are those entirely compatible with temporary ischemia of the tissue, and are not explainable on the basis of any evident vascular lesion. The inference, of course, is that the air which had originally obstructed the vessel had been carried away by the circulation following the release of the initial vasospasm (to be referred to later) but before the death of the individual. This is a phenomenon well-known in animal experimentation with air embolism, and examples will be included in the experiments reported by us herein.

There has been much experimental work which has provided strong evidence for arterial air embolism, especially that of Wever,¹⁶ Schlaepfer,¹⁸ and Rukstinat.¹⁹ This evidence has shown that air need not be extrinsic (that is, introduced from without through the chest wall) in order for air embolism to occur. A broncho-venous fistula, for example, is a very possible intrinsic source for the air, as will be pointed out later.

As a result of all these facts, the present opinion of most phthisiologists and chest surgeons appears to be that, while pleural shock is a possible explanation for milder episodes, the serious accidents are probably due to air embolism in most instances.

ETIOLOGY

It was formerly believed that the air responsible for arterial air embolism either was injected from a pneumothorax apparatus, or, in the case of thoracic surgery, was aspirated into open pulmonary veins. However, cases occurred not infrequently in pneumothorax work in which no air had been injected when the accident occurred. This led some investigators to suggest that there was sufficient air in the pneumothorax tubing to be aspirated into a vein having a negative intravascular pressure. The fact that small amounts of air may result in serious accidents in experimental work supported this possibility. However, there still remained no explanation for the cases which complicated the tapping of pleural effusions, in which no such extrinsic air source could be implicated, the type of case which Capps¹⁰ had used as an argument against air embolism. This difficulty, however, was resolved when it was realized that air already present in the thoracic cavity could be a very important source of accidents,

in the event that the therapeutic procedure provided access of air to the venous system, and that the pressure gradient from source to vein was sufficient. It is possible, therefore, to classify the sources of air in arterial air embolism as follows:

Intrinsic:

1. Air in the alveoli
2. Air in pulmonary cavities
3. Air in the pleural cavity (pneumothorax)

Extrinsic:

1. Injected air
2. Air aspirated from the tubing of the pneumothorax apparatus
3. Air aspirated into pulmonary veins during open-chest procedures

In pneumothorax work, injected air may reach a pulmonary vein *directly*, since there is considerable opportunity for the needle to enter pulmonary tissue, especially during an initial treatment, but it is also possible for the air to reach such a vein *indirectly* if the pressure in the pneumothorax cavity is raised sufficiently to tear an adhesion with the production of a pleurovenous fistula.

Air from intrinsic sources cannot reach the pulmonary veins unless the trauma of the thoracic procedure produces an opening from the source to the vein. In addition, there must be a sufficient pressure gradient from source to vein, as well as some factor to maintain the patency of the opening. Infiltration of lung tissue is probably the additional factor which, in most cases, prevents the closure of the fistulous opening.¹⁸ The necessity for such a concatenation of circumstances explains the rarity of accidents when needles are introduced into *normal* lung tissue.

After the air, from either an extrinsic or an intrinsic source, has entered the pulmonary vein, it is carried to the left heart and on into the aorta. From this point its route is determined to a considerable extent by the position of the patient. Air buoyancy will, of course, tend to cause the gas to enter those branches of the aorta which are superiorly oriented with relationship to the trunk of the vessel.²⁰ Thus, if the coronary and cerebral vessels are directed upward from the aorta, these circulations will receive portions of the air. If, on the other hand, the head of the patient is below the level of the body, air will not enter the cerebral circulation. It is obvious that, if such a position is to be used to avoid cerebral involvement, it must be used prophylactically rather than following the embolization. There remain, however, definite possibilities for the use of this principle in therapy, and these will be discussed later.

When air has reached the terminal arterial branches of an organ, the effects produced are the result not only of the mechanical obstruction of the smaller vessels, but also of a neurovascular mechanism producing vasoconstriction. It has been shown by the splendid experimental work of Chase¹⁷ that air emboli represent moderate or strong vascular irritants which produce a series of effects in all respects similar to those induced by other mechanical, chemical, or bacterial irritants. Therefore, it is possible to understand why the ischemic effects are greater than would be expected on the basis of the size of the embolus alone.

Such a neurovascular mechanism is also, of course, a well-recognized part of the pathologic physiology of solid emboli.

PARADOXICAL AIR EMBOLISM

While it is generally true, as has been stated in the opening paragraph of this paper, that pulmonary air embolism and arterial embolism are distinct entities, cases have been reported in which a mixture of the two types has been evident. Thus, air which has entered systemic veins has produced manifestations not only of pulmonary but also of arterial embolism, and at post-mortem examination air has been found in the cerebral and coronary arteries.

In two of the cases reported, the reason for this has been obvious, an interauricular septal defect having been found at autopsy. In one of these,²¹ during a radical mastectomy for carcinoma in a 37-year-old woman, a loud sucking noise was heard which began simultaneously with the severing of a branch of the axillary vein. Vascular collapse was immediate and death resulted within half an hour. At post-mortem examination the right auricle was distended with gas. Numerous small gas bubbles were observed in the coronary, mesenteric, and internal mammary arteries. There were two interatrial septal openings, 1.4 cm. and 0.3 cm. in diameter. The authors believed that the pulmonary air embolism resulted in a rise in the pressure within the right heart and that this produced a veno-arterial shunt through the septal defects, with the entrance of air into the systemic arterial system.

In another case,²² a 25-year-old woman attempted to induce abortion by blowing air into the uterus. Following this she became unconscious and had repeated convulsions. Two days later she recovered from the coma, but was found to have a left hemiparesis. Later she developed manifestations of pelvic sepsis, and died eight weeks after the accident. At post-mortem examination an interauricular septal defect which admitted the tip of the finger was found. In this case it is likely also that the mechanism responsible for her coma, convulsions, and left hemiparesis was paradoxical air embolism through the septal defect.

In other instances no septal defect has been reported, and the mechanism is not clear. Thus, in one case among four in which air embolism had resulted from attempts to procure abortion by means of a Higginson type of syringe,²³ air was found in the coronary vessels. In a case reported by Weyrauch,²⁴ collapse followed perirenal air insufflation. The clinical picture was that of a combination of pulmonary and arterial air embolism. Death occurred twenty-one hours after the accident. At autopsy the findings in the brain were similar to those observed in animals which have died some time after cerebral air embolism. There is no statement in this report concerning the character of the interauricular and interventricular septa. In still another case providing an example of embolism involving both systems, Mylks, Brown, and Robinson²⁵ describe an instance in which death terminated labor after an unsuccessful attempt at artificial induction. At post-mortem examination air was found in the vessels of the breasts and in the right heart cavity.

In cases reported by Warring and Thomas²⁶ and by Bohorfoush,²⁷ air was found post mortem in the cerebral *veins*, but not in the arteries. In those

reported by the former, air was found in the coronary veins as well. Bohorfoush has suggested venous transmission of air as an explanation for these and other paradoxical cases. He points out that air injected into either the vertebral vein or vena caval system might reach the cerebral veins by a totally venous route when the patient is in an upright position. This would explain some instances of cerebral air embolism in which symptoms developed only after the patient had sat up or stood up following an injection. Whether gas in the cerebral veins could be responsible for manifestations of ischemia has not, to our knowledge, been demonstrated experimentally.

The possibility that air might pass the pulmonary circulatory filter and reach the systemic arterial circulation has been suggested. That this can happen experimentally we have demonstrated in the dog. This is especially true in experiments wherein repeated sublethal doses of air are injected into the systemic veins, with the animal on the left side. When the animal is on the right side, air never reaches the systemic circulation, evidently because the air trap in the outflow tract of the right ventricle is most effective in this position. Whether conclusions from experiments such as these can be carried over to the conditions under which human air embolism occurs is uncertain. Certainly further experimental work is needed on this subject before definite conclusions can be drawn.

CLINICAL MANIFESTATIONS

The clinical manifestations of arterial air embolism are somewhat varied, but there are many features which are common to the majority of cases reviewed in the literature. The onset may be very sudden, but in quite a few instances there are warning symptoms just before the severe features become manifest. The patient will often state that he "feels funny," that he is dizzy, or that he feels faint. Fear of death is mentioned by some. Rarely, pain in the head is the first complaint. These initial features of the embolism may come on during the thoracic procedure, and it is often noted that when the needle is withdrawn the tip is bloody. In some cases, however, the onset is not immediate but develops when the patient arises from the operating table, or, occasionally, even hours later.

Following the early warning symptoms there is usually loss of consciousness, the duration of which is variable. Some patients retain consciousness entirely, but may be disoriented. Convulsions, localized or generalized, tonic or clonic (often both in sequence), occur in somewhat less than half the cases. Following the return of consciousness, or sooner in some cases, various localized neurological signs may be noted. These include hemiplegia, hemiparesis, hemianesthesia, monoplegia, hemianopsia, nystagmus, and strabismus. Frequently these signs disappear within a few hours or days, but cases have been recorded in which a hemiparesis persisted for as long as four months. Blindness may also occur, and it may be complete even in patients who have not temporarily lost consciousness. This manifestation may persist for several days. The pupils are usually dilated, and sometimes widely so, but occasionally they are constricted. Cyanosis is noted in the majority of instances. It has been described in some as being limited to the face and neck, but usually it is generalized, and

may be very marked. Respiratory disturbances are usually present. Most often there is slowing of the respiratory rate, and sometimes Cheyne-Stokes breathing is observed. Manifestations of peripheral vascular collapse, including thready or imperceptible pulse, marked drop in blood pressure, and cold, clammy, pallid skin, are frequent, and may be severe even in patients who later recover. The heart has been described in some cases as sounding tumultuous, but mill-wheel murmurs, such as are heard in pulmonary air embolism, are not encountered. Following recovery from the acute episode, should the patient be so fortunate, pain in the chest, often referred to the precordial or substernal area, is a frequent complaint, and this may be accompanied by considerable dyspnea. Nausea or vomiting may also occur. These complaints may persist for hours or days.

In one patient²⁸ electroencephalographic study was carried out during the early phases of recovery, and abolition of normal cortex activity was noted.

PATHOGNOMONIC SIGNS

The clinical features so far referred to are, of course, nonspecific in that they may occur in other disease states. There are, however, five features which may be regarded as specific or pathognomonic. These require stress since they are known to few physicians, and their diagnostic value is so great that search should be instituted for them in every case in which there is a possibility of arterial air embolism.

1. *Detection of Air in the Retinal Vessels by Ophthalmoscopic Examination.*—This is perhaps the most important of the specific signs.¹²⁻¹⁶ Bubbles may be seen streaming through these vessels, or there may be pale, silvery sections in them representing columns of air. These findings are often quite temporary and should therefore be searched for immediately after the onset of the accident. Reyer and Kohl¹⁶ state that this sign has been observed in one of ten cases of arterial air embolism. Following the disappearance of the air bubbles or columns, pallor of the retina may be noted for several days, and this may be associated with diminution or loss of visual acuity.

2. *Liebermeister's Sign.*—In a series of cases observed by Liebermeister,²⁹ it was possible for him to declare the presence of emboli very early by the occurrence of sharply defined areas of pallor in the tongue. He ascribed this phenomenon not to vasoconstrictor stimuli but to abridging of arterial flow by air bubbles in one or the other of the lingual vessels or of their branches. The position of the anemic sectors depended on the branch of the lingual artery which was blocked. If it was an end branch of the right lingual artery with the stem remaining free, there appeared a small segmentary anemia on the edge of the tongue to the right of the tip; if the whole stem became blocked there was a total anemia of the right half of the tongue. He believed that this sign was not only an early one but also a constant one, that its presence was an almost certain indication of air embolism, and, conversely, that its absence was as clear an indication that air embolism was not present.

We are aware of no instances in the American literature in which this sign has been described, perhaps because it is not generally known, and it is certainly very likely to be missed in the confusion that surrounds the catastrophic episode

unless the physician is aware of its occurrence and importance. In the British literature a case is reported³⁰ in which attacks of air embolism occurred in the same patient on two different occasions, during both of which there appeared a temporary *right* hemiparesis and *right-sided* pallor of the tongue. Certainly the involvement of the tongue on the same side as the hemiparesis (the opposite side to the involved motor centers) is difficult to explain on the basis of air embolism of the lingual artery, and raises the question of vasospastic phenomena associated with air embolism, as previously referred to in connection with the studies of Chase.¹⁷

3. *Marbling of the Skin*.—This interesting dermal manifestation is due presumably to embolism of the skin vessels, and is noted especially over those portions of the body which are superiorly located.

4. *Air Bleeding*.—Van Allen and Hrdina²⁰ have stressed the value of this diagnostic sign. In a case of suspected air embolism a small incision is made in the skin over the most superior portion of the body. Air bubbles may then be observed in the blood escaping from this incision.

5. *Roentgenologic Demonstration of Air in the Cerebral Vessels*.—This sign has been reported in only one case.¹⁷ It is probable that amounts of air sufficient to become thus demonstrable will be rapidly fatal, as in the one case referred to, and this sign will therefore have its main value as a means of post-mortem diagnosis.

CORONARY INVOLVEMENT

That the coronary arteries are frequently involved in arterial air embolism has been demonstrated by experimental and post-mortem studies. Rukstinat and LeCount³¹ produced bronchovenous fistulas in guinea pigs by raising the intratracheal pressure sufficiently high to rupture alveoli into adjacent blood vessels. Convulsions were invariably produced when the pressure was raised to 30 mm. Hg, and a pressure of 45 mm. Hg always resulted in death in fifty to seventy-five seconds. Necropsy carried out under water revealed air in the coronary arteries in all the animals. There was a 50 to 90 per cent filling of these channels with the air. Hemorrhages were noted in the myocardium in some instances. Rukstinat¹⁹ later reported experiments in which air was injected rapidly into the coronary arteries of dogs. This was followed by tumultuous heart action and acceleration of rate, giving way to a pronounced slowing within ten to twenty seconds. Death occurred in one to four minutes. Air injected slowly in amounts up to 20 c.c. caused only temporary disturbances. No statement is made as to whether or not infarcts developed in any of the animals which recovered, and no electrocardiographic studies were carried out. Air injection into the left auricle caused death from coronary air embolism in thirty-five to seventy seconds. Left auricular injections were likewise fatal in a group of animals in which the carotid and vertebral arteries had been ligated fifteen minutes previously in order to eliminate cerebral embolism as a factor in the fatal outcome. Rukstinat concluded from his experiments that obstruction of the coronary arteries must be considered of great importance in all cases of air embolism originating in the pulmonary circulation.

In 1929, Van Allen and Hrdina²⁰ performed pulmonary vein air injection experiments which showed that coronary involvement was the cause of death in animals when cerebral involvement was prevented by the head down position. They calculated that the maximum tolerated dose of air was 0.5 c.c. per kilogram of body weight for animals with the head up, 1.5 c.c. per kilogram with the head horizontally placed, and 3.3 c.c. per kilogram with the head down.

Moore and Braselton^{32,33} demonstrated conclusively that in cats the cause of death following air embolism by way of the pulmonary vein was obstruction of the coronary arteries. A dose of air amounting to 0.5 c.c. per pound of body weight caused typical coronary death upon every experimental attempt. Death resulted regardless of the position of the animal. The heart was found to behave exactly as when the coronary arteries were ligated. Pure carbon dioxide injections were found to be well tolerated, however.

Kent and Blades³⁴ injected 1.0 c.c. of air into the pulmonary vein of twenty-eight dogs and found this to be universally fatal. The coronary arteries became filled with air bubbles which did not progress along the course of the vessels. After variable intervals of time the heart began to have weaker contractions, the heart rate increased, and the ventricles dilated slightly. Shortly thereafter, ventricular fibrillation always occurred. Within a variable period of time the heart became markedly dilated and the animal died. In another group of animals 0.25 c.c. of air was always tolerated, but 0.5 c.c. resulted in a mortality rate of 50 per cent, with death occurring as described for the animals which received 1.0 cubic centimeter. When the animals were injected with the body in a vertical position, head down, 8 to 14 c.c. could be tolerated, the air being trapped in either the auricle or ventricle until sufficient had been injected to be forced by ventricular contraction into the aorta. Kent and Blades have tended to discount the importance of cerebral involvement in air embolism as a result of their findings in other experiments, in which they injected as much as 20 c.c. into the carotid artery of dogs without demonstrable effect. However, it should be pointed out that, differing from man, the dog is able to tolerate ligation of both carotid arteries and both vertebral arteries without evidence of cerebral damage.⁴⁸

Reports of coronary air embolism in the human subject are few in number, possibly because the interest of the observer has been centered on the cerebral manifestations. Jackson and Babcock³⁵ reported a case in which sudden death occurred during an open operation for empyema in a 23-year-old man. There was systolic arrest of the heart. This, the authors believed, was due to coronary air embolism, although no statement is made as to the actual observation of air in the coronary vessels.

Pollak³⁶ reported a case in which the coronary vessels were filled with air at the time of the post-mortem examination. The patient had developed a spontaneous pneumothorax, which was treated by the aspiration of air. One hour following the aspiration, the patient suddenly collapsed and became markedly cyanotic. Death ensued a few hours later.

The case reported by Chase,¹⁷ and previously referred to as having demonstrated air filling of the cerebral vessels by roentgenologic examination, also showed filling of the coronary vessels at post-mortem examination. The patient,

a man 25 years of age, underwent middle lobe lobectomy for bronchiectasis. During the course of the operation the main pulmonary vein was inadvertently cut, and there was a brisk hemorrhage accompanied by a whistling inspiratory sound. It took about fifteen seconds before the Kocher clamp could be applied to the bleeding vessel. Within a minute the anesthetist reported that the pulse rate had fallen to 40 and that the blood pressure had risen to 160 systolic. Within three minutes of the hemorrhage, the patient was declared dead.

In a case reported by Hall³⁷ a 24-year-old man with pulmonary tuberculosis collapsed during the refill of a pneumothorax pocket, developed nystagmus and strabismus, and complained of "anginal symptoms similar to those of coronary occlusion." He then became unconscious, and died thirty minutes later. At autopsy, air was found in the left side of the heart, and in the coronary, celiac, renal, hepatic, and mesenteric arteries. No examination of the head was done.

Schattenberg and Ziskind¹² describe the case of a 46-year-old man who, while receiving his seventh pneumothorax refill, and just as the needle was being withdrawn, developed cyanosis of the face and neck, together with marked air hunger. Air bubbles were observed in the retinal vessels. Death resulted within a few minutes despite the intracardiac injection of epinephrine. At post-mortem examination the left auricle and left ventricle were dilated and filled with extremely frothy blood. The coronary arteries contained a number of gas bubbles. Air was also found in the basilar and carotid arteries and in many of their branches.

Still another instance of the observation of air in the coronary arteries at post-mortem examination has been referred to previously in the discussion of paradoxical air embolism (air embolism associated with mastectomy).

In all of these cases in which air has been reported in the coronary arteries, no evidence of infarction of the myocardium has been described. This is understandable since the time was insufficient for infarction to have become evident either grossly or microscopically. The case reported by Bratkov and Verdnikova³⁸ is therefore especially interesting. Their patient was a 26-year-old man who had pulmonary tuberculosis. Pneumothorax therapy on the left was attempted, and on the third treatment, after 100 c.c. of air had been introduced, the patient complained of dizziness and loss of sensation in the right arm. The needle was immediately withdrawn. The pulse became very weak and finally disappeared entirely, the respiration nearly stopped, and there was dilation of the pupils and loss of consciousness. Following artificial respiration and cardiac stimulants, he regained consciousness, but complained of weakness, pain in the cardiac region, and headache. The pain became gradually more severe, marked dyspnea was noted, he was "morbidly pale," and there was cyanosis. The heart sounds were feeble, the pulse was thready, and there was evidence of edema at the lung bases. Death ensued twenty-one hours after the occurrence of the embolism. At post-mortem examination several dark, cherry-red plaques (2 by 3 cm.) were seen through the epicardium on the anterior surface of the heart. The cardiac muscle was flabby. The chambers were filled with blood clots. The valves were normal in appearance. On section, the myocardium of the left ventricle had several areas of diffuse hemorrhagic infiltration involving the whole thick-

ness of the cardiac muscle and giving rise to the appearance of the plaques described. The coronary arteries showed no pathologic changes. Infarction of the myocardium of the left ventricle was diagnosed, the basis for the infarction being coronary air embolism.

A similar case was described in 1935 by Farr,³⁹ in which cerebral manifestations developed during pneumothorax therapy, and on post-mortem examination foci of hemorrhage and myomalacia were found in the myocardium.

Electrocardiographic Evidence.—Very few cases have been reported in which electrocardiographic examination has been done. This is probably due to the fact that attention has been centered mainly on the cerebral manifestations, and, in some instances, death has occurred before such an examination could be attempted.

The first case which we have been able to find in the literature in which electrocardiographic evidence of myocardial infarction has been presented is that of a 24-year-old woman with pulmonary tuberculosis, reported by one of us in 1935.⁴⁰ Prior to pneumothorax therapy, this patient had had an electrocardiographic examination because of a systolic basal murmur. This electrocardiogram served as a control for the tracings taken after the accident which occurred on a fourth unsuccessful attempt to induce a left pneumothorax. The needle had just been introduced, and no manometer oscillations had been obtained, when the patient complained of feeling faint. The needle was immediately withdrawn, but a generalized convulsion lasting about thirty seconds ensued. Following this, the patient was markedly cyanotic, there was slowing of the respirations, and the pulse could not be felt. Stimulants were administered, and, following recovery of consciousness, the patient complained of substernal pressure. There was marked dyspnea and frequent vomiting. The substernal pressure and vomiting persisted for several hours, and the dyspnea for six days. Following this there were no further symptoms referable to the incident, and the tuberculous lesion eventually became quiescent. The electrocardiographic changes which followed the accident were of great interest. Unfortunately, precordial leads were not done routinely in 1935, but the standard leads showed a large Q wave in Lead I, elevation of the RS-T segment in Lead I, and depression of the RS-T segment in Lead III in the tracing taken three hours after the embolism. Two days later the deviations of the RS-T segments had largely disappeared, but the large Q wave in Lead I persisted and there was then present a coronary type of T wave inversion in Lead II. In a tracing taken thirteen months after the accident there was a reappearance of the initial upstroke of the QRS complex in Lead I, and the T-wave changes had disappeared. The findings were then identical to those in the control tracing prior to the accident.

The case reported by Cameron⁴¹ is of interest in that the electrocardiographic changes which developed following an attempt at pneumothorax induction in a 24-year-old woman with tuberculosis included temporary complete heart block and intraventricular block (the QRS interval was 0.12 second). There was marked elevation of the RS-T segment in Lead I, slight depression in Lead II, and moderate depression in Lead III. Later the T wave in Leads I and IV R became inverted. Eventually there was a complete reversion to normal.

EXPERIMENTAL STUDIES

Since there is a lack of data in the literature demonstrating whether air introduced experimentally into the coronary circulation can produce ischemic areas in the myocardium or electrocardiographic changes such as would explain the changes observed in the two cases referred to in the immediately preceding two paragraphs, we have carried out a series of eighteen experiments using sixteen dogs. Sodium pentothal, 20 mg. per kilogram of body weight, and sodium barbital, 150 mg. per kilogram of body weight, were administered intravenously for anesthesia. The thorax was opened by a sternum-splitting incision. Electrocardiographic leads were taken from various epicardial areas by means of a wick electrode. The indifferent electrode was attached to the left hind leg. The galvanometer connection was such that positivity of the exploring electrode was represented by an upstroke on the record.

In fourteen experiments air was injected into the anterior descending branch of the left coronary artery. In two of these experiments (Experiments 8 and 9) it was injected not into the main trunk of this artery, but into small branches distributed to the left ventricular muscle. In the other four experiments the air was injected either into the left auricle (Experiment 11) or into the pulmonary vein (Experiments 5,*a*, 14,*a*, and 15). In most of the experiments in which air was injected into the left anterior descending artery or one of its branches, the artery was dissected from its bed for a distance of approximately 1.0 cm. so that it could be lifted gently by ligatures in order to facilitate the introduction of the needle into the lumen. Care was taken in each instance, however, to make certain that ischemia of the myocardium was not induced by this procedure, and the duration of the time during which the artery was under any constricting tension was very short. In three experiments (Experiments 13, 14, and 16) no arterial isolation was carried out, the needle being introduced into the artery during a period of asystole induced by vagal stimulation. No electrocardiographic evidence of ischemia of the myocardium resulted from this procedure.

Data summarizing the series of experiments are included in Table I. Gross evidence of ischemia of the myocardium was observed in every experiment following the injection of air, and the site of the ischemic area depended upon the branch or branches of the artery involved by the bubbles. This, in turn, was determined by the principle of air buoyancy, air tending to enter the most superiorly located vessels. The ischemia was evidenced by a cyanotic appearance of that portion of the myocardium involved by the vascular obstruction in every instance but one. In Experiment 5,*a*, in which 10 c.c. of air was injected into the pulmonary vein, there was extensive filling by air of the entire anterior descending artery and all of its branches to the left ventricle; and, in this instance, the ischemia was manifested by *pallor* of the left ventricular muscle. A high grade of intraventricular block developed promptly, followed by complete heart block and death within a few minutes (Fig. 1). In many of the experiments in which the animal recovered, the air rapidly disappeared from the involved vessel and the manifestations of ischemia disappeared. However, in two experiments (Experiments 9 and 11), the ischemia persisted following the disappearance of the air and was still present when the animal was sacrificed one

hour later. These two instances are important in a consideration of the cases of human subjects in which evidence of myocardial infarction has been found to persist after the air responsible for the vascular obstruction has presumably disappeared.

TABLE I. SUMMARY OF ARTERIAL AIR EMBOLISM EXPERIMENTS

EXPERIMENT	DOSE (C.C.)	ISCHEMIC AREA	LEAD	ELECTROCARDIOGRAM		T WAVE	RECOVERY OR DEATH
				PROLONGED QRS	RS-T SEGMENT		
Injection Into Left Anterior Descending Artery or Branch							
1	1.0	L.V.	L.V.	+	0	—	R
2	0.5	L.V.	R.V.	0	0	0	D
3	0.5	L.V.	R.V.	0	—	0	R
4	1.0	L.V.	L.V.	+	+*	0	R
5	0.5	L.V.	L.V.	+	+*	0	R
6	0.5	I.V. groove	L.V.	+	0	+	D
7	0.5	L.V.	L.V.	0	+*	+	R
8	0.5	L.V.	L.V.	0	—	0	R
9	0.5	L.V.	L.V.	+	+*	—	Sacrificed
10	1.0	L.V.	R.V.	0	+ —	—	D
			L.V.	0	— +	—	
12	0.25	L.V.	R.V.	0	+ (slight)	0	R
			L.V.	0	+*	0	
13	0.05	R.V.	R.V.	+	+	—	D
14	0.025	R.V.	R.V.	0	0	+	R
16	0.05	R.V.	R.V.	0	0	—	R
Injection Into Pulmonary Vein or Left Auricle							
5a	10.00	R.V.	L.V.	+	—	0	D
11	5.0	L.V.	R.V.	0	+ (slight)	0	Sacrificed
			L.V.	0	+*	0	
14a	10.0	R.V. and L.V.	R.V.	+	+*	—	D
15	5.0	R.V.	R.V.	0	+*	+	R
Upward deviation of the RS-T							

Upward deviation of the RS-T segment is represented by a plus sign; downward deviation, by a minus sign; no deviation, by a zero. Augmentation of the positivity of the T wave, or a shift toward positivity of an originally inverted T wave, is represented by a plus sign. The appearance of T-wave inversion, or definite augmentation of negativity, is represented by a minus sign.

L.V., left ventricle; R.V., right ventricle; I.V., interventricular.

*Experiment in which electrode was located over the ischemic area.

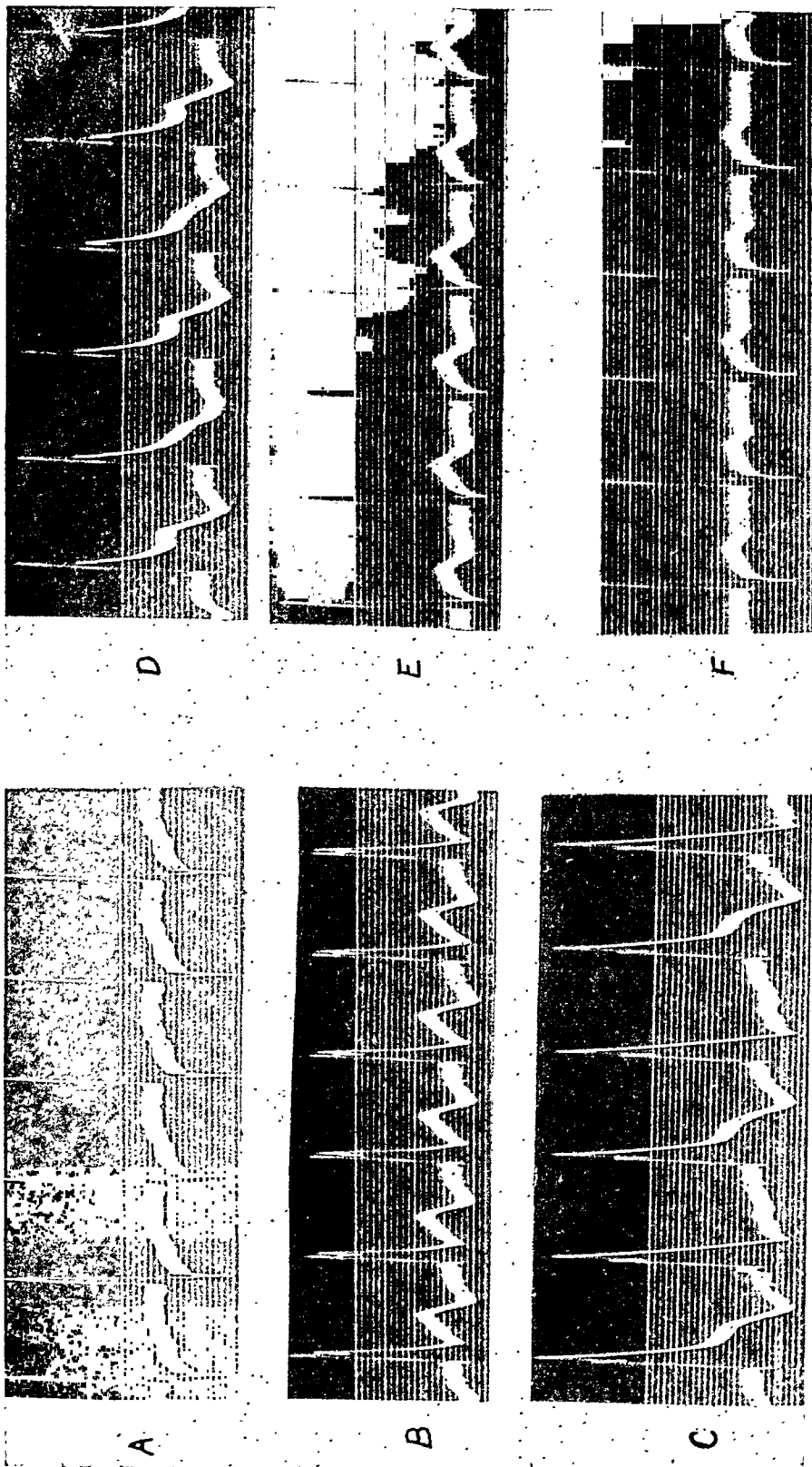


Fig. 1.—Experiment 5. Weight of dog, 4.5 kilograms. Lead from left ventricle 2.5 cm. above apex. Indifferent electrode on left hind limb. Standardization 3/10 normal. Camera twice normal speed. Time lines omitted for clarity in reproduction. Positivity of exploring electrode represented by upstroke.

A, Control, B, C, and D, Tracings taken within a few minutes after the injection of 0.5 c.c. of air into the left anterior descending coronary artery. Note marked widening of QRS complexes with notching, and elevation of RS-T segments. E and F, taken during recovery. Bubbles had disappeared from artery. Animal recovered.

In six of the experiments, death of the animal occurred soon after the introduction of the air, the final cause of exodus being ventricular fibrillation. It is difficult from the data at hand to relate the mortality in these experiments to the dosage injected. In Experiments 5,*a* and 14,*a* large amounts of air (10 c.c.) were injected into the pulmonary vein, and extensive filling of the ventral coronary system was noted; hence the death of these animals was not unexpected. The largest dose injected directly into a coronary artery was 1.0 c.c., and this was done in three experiments, one resulting in death, the other two in eventual recovery. Death occurred in two instances out of seven in which 0.5 c.c. was injected. In these seven animals there was some relationship of the mortality to the size of the animal: the smaller animals (10 pounds) succumbed, but two other animals of similar weight recovered from this dose. In one experiment death occurred following a dose of only 0.05 cubic centimeter. This was in one of three experiments in which air was injected into the coronary artery without preliminary dissection of the artery, and in each of these instances the heart was slightly rotated so that the air entered the right branches of the anterior descending artery. It is possible that the development of ischemic effects in the three experiments in which such small amounts of air were injected was due to the smaller number of right ventricular branches, which allowed more air per branch. One can only speculate whether the right ventricular muscle might be more susceptible to the effects of such obstruction. Whatever the reason, it is important to emphasize that small amounts of air in the coronary circulation *may* have disastrous results.

Electrocardiographic Changes.—It will be noted from Table I that RS-T segment changes were observed in twelve of the experiments. The direction of the deviation of this segment was in accordance with previously recognized principles concerning current of injury detected at the epicardial surface.⁴² When the electrode was over the ischemic area (Experiments 4, 5, 7, 9, 11, 12, 13, 14,*a*, and 15) an upward deviation of the RS-T segment was invariably found. This was often of marked degree, as is seen from Fig. 2. When the electrode was distant from the ischemic area, depression of the RS-T segment was noted in three instances (Experiments 3, 5,*a*, and 8, Fig. 1). It is of interest that in one (Experiment 10), in which simultaneous leads were taken from the two ventricles, the electrodes were so placed that each was very close to the two opposite edges of the ischemic area. The right ventricular electrode showed first an elevation and then a depression of the RS-T segment, and the left ventricular electrode showed the reverse, the changes in the two at all times being reciprocal.

T-wave changes were more difficult to analyze. High T waves such as may be seen during certain phases of myocardial ischemia⁴³ were observed in Experiments 7 and 15, in each of which the electrode was over the area of ischemia. In Experiments 6 and 14, a previously negative T wave became upright. Definite inversion of the previously upright T wave occurred in Experiments 1, 9, 10 (both ventricles), 13, and 14,*a*. In Experiment 16 the T wave was flattened. In three of these (Experiments 9, 13, and 14,*a*), the electrode was over the ischemic area and in Experiment 10 the two electrodes were very close to its margin. The lack of T-wave inversion in the other instances in which the electrode was

over the area of injury is undoubtedly related to the fact that RS-T segment changes were present.

Prolongation of the QRS complex was noted in eight of the experiments. Whether this was due to a local intraventricular block in the injured area or to bundle branch block was not determined. It is unfortunate that in the three experiments in which leads were taken simultaneously from both ventricles, prolongation of the QRS complex did not occur.

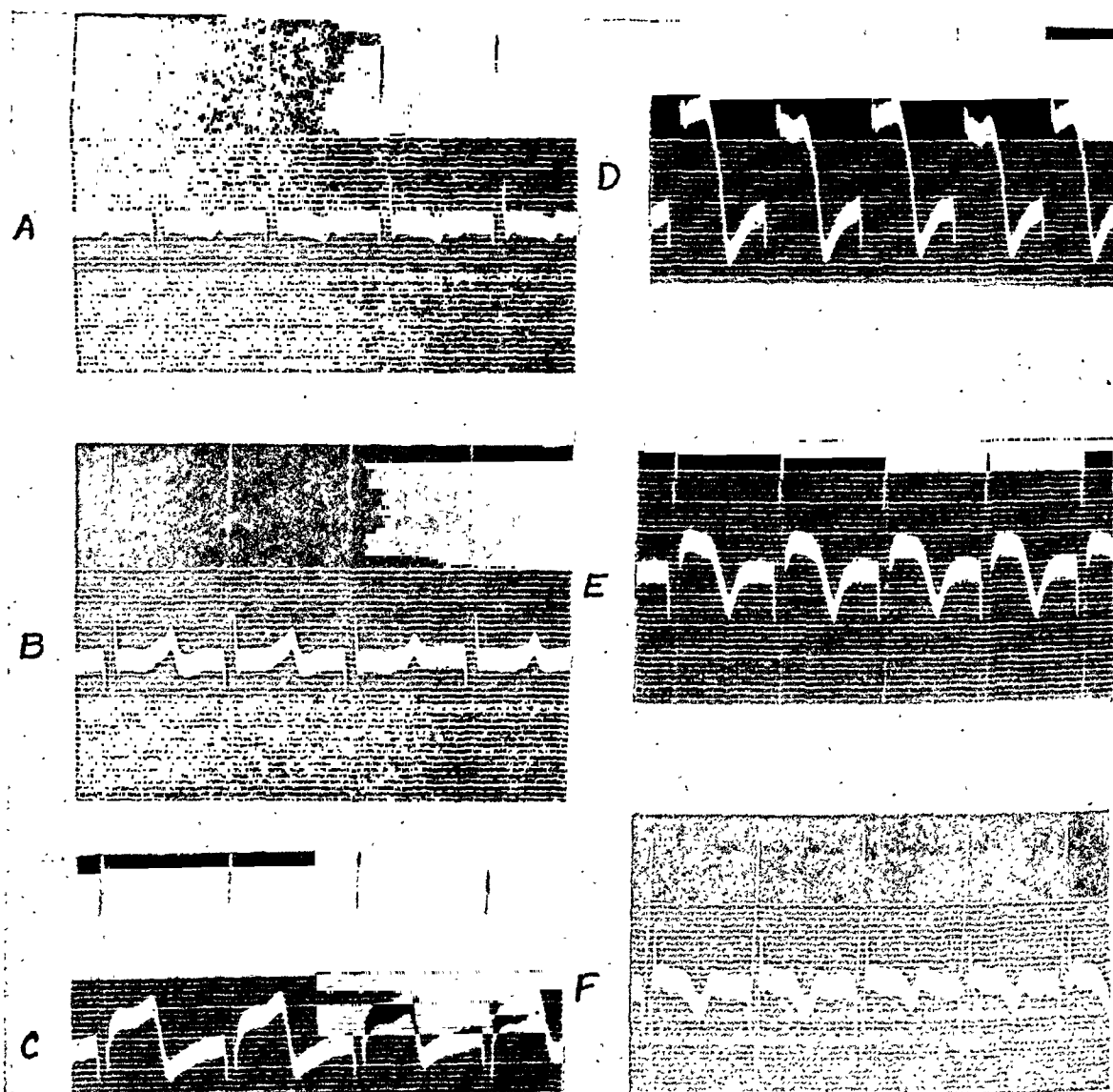


Fig. 2.—Experiment 9. Weight of dog, 5.9 kilograms. Lead from left ventricle 1.0 cm. above apex. Indifferent electrode on hind limb. Standardization 3/10 normal. Camera speed twice normal. Time lines omitted for clarity in reproduction. Positivity of exploring electrode represented by up-stroke.

A, Control. B, C, and D, Tracings taken within a few minutes after the injection of 0.5 c.c. of air into a small apical branch of the left anterior descending artery. Note early sharp rise in T waves, followed by increasing elevation of the RS-T segment.

E and F, Representative tracings taken during period of one hour following injection. Area of cyanosis in region of exploring electrode persistent despite disappearance of air bubbles from artery. Note T-wave changes and large initial negative deflection of the QRS complex.

It is of especial interest that in one animal (No. 9, Fig. 2) a large Q wave developed during the course of the experiment. This was one of the two animals in which a persistent area of ischemia resulted from the air injection. This fact may indicate late activation of the endocardial surface in the area of ischemia, or it may be evidence of infarct formation.

Other electrocardiographic effects noted were electrical alternans in one experiment (Experiment 5,a), bigeminal rhythm in two (Experiments 1 and 7), and complete A-V block in one (Experiment 5,a).

COMMENT

It is certainly possible, as a result of these experiments, to state that air is not well tolerated within the coronary circulation of the dog, as ischemic areas were induced within the myocardium in all of the experiments, and death occurred in six of the eighteen animals. The changes observed electrocardiographically are identical with those observed in instances of ischemia induced by other means, such as ligation of the coronary arteries. The ischemia induced by air can probably be related to both of the factors elucidated by Chase,¹⁷ that is, vascular obstruction and vascular spasm, although no attempts were made in our experiments to show the presence of vasospasm. The effects of the vascular obstruction may be very transient, the air being rapidly disposed of, but in some instances it may be sufficiently prolonged to result in persistent ischemia of the myocardium even after air bubbles can no longer be detected within the lumen of the vessel involved. Thus it is possible to explain those instances of air embolism in the human being in which evidence of myocardial infarction is found some time after the embolic accident, when it must be inferred that obstructing air can no longer be present.

The importance of the principle of air buoyancy was demonstrated by the experiments, in that the air filled the superiorly located portions of the coronary circulation. The importance of the application of this principle by use of the head down position in the prevention of cerebral air embolism has been demonstrated by the experiments of Van Allen and Hrdina.²⁰ It would seem very logical to assume that the same principle could be applied effectively to the prevention of coronary involvement. Since in the human being the right coronary artery arises anteriorly from the right aortic sinus, and the left coronary artery arises mesially from the left posterior aortic sinus, it should be possible to prevent the entrance of air into these vessels by placing the patient in a position midway between left lateral and prone. However, in order for this technique to be effective, the patient must already be in this position when the air reaches the aorta. This would appear on first consideration to nullify the practical value of this maneuver, since, by the time the patient gives a warning that air embolism has occurred, air has probably already reached the coronary and cerebral circulations. However, there is indication from a consideration of the cases reported in the literature that the initial dose of air may not be the only one, since a fistula between the pulmonary vein and a pneumothorax, or other air-containing cavity, may be opened and closed repeatedly, and the pressure gradient between the source of the air and the vein may fluctuate sufficiently to produce repeated em-

bolism. Hence, if warning is given of the occurrence of air embolism, and the initial dose is not fatal, it would appear to be very logical to place the patient immediately in the favorable position described so that any subsequent embolization may not have serious effects. In order to prevent cerebral embolism the patient should also be placed so that the head is down. It would seem wise to maintain such a position for a period of several hours in order to allow sufficient time for healing of the fistulous tract to occur. The position would not be an uncomfortable one for the vast majority of patients.

Obviously, any reliance upon the use of this position should not exclude the use of other established principles in the treatment of air embolism, namely, the use of careful technique in chest procedures in order to avoid embolism, and the administration of 100 per cent oxygen as therapy after embolism has taken place. The value of the latter has been demonstrated by the studies of Fine and co-workers^{44,45} and Kelly and co-workers.²⁸ It is well known from studies dealing with decompression sickness that it is possible to "wash out" the nitrogen in body tissues by means of oxygen inhalation.⁴⁶

In conclusion, a few words would be appropriate concerning the value which may be attached to the use of other gases, more soluble than air, in an attempt to prevent air embolism in pneumothorax work. Oxygen has been suggested for this purpose, but the solubility of oxygen is only slightly greater than that of air, and we have found it almost as dangerous as air itself in our studies of pulmonary air embolism. Presumably the same would hold true for arterial air embolism. Carbon dioxide, on the other hand, is approximately twenty times as soluble as air and would therefore be far better tolerated if transported in the blood stream. This has been shown in our work in pulmonary air embolism⁴⁷ and also in the work of Moore and Braselton³³ in connection with arterial air embolism. However, it should be emphasized, as has been mentioned earlier in this communication, that it is often not extrinsic gas which is responsible for the embolic accidents, but rather air contained within the body which enters the pulmonary vein through a fistulous opening. Hence, only those accidents in pneumothorax in which the injected gas enters the vein would be prevented by the use of carbon dioxide. Furthermore, the speed of absorption of carbon dioxide makes it an undesirable gas for pneumothorax work.

SUMMARY

Arterial air embolism is an infrequent but often disastrous complication of various thoracic therapeutic procedures. Occasionally it may result paradoxically from air entering the systemic veins and reaching the systemic arteries through a septal defect, or possibly by other mechanisms. The serious manifestations are the result of obstruction by air bubbles of cerebral and coronary vessels, together with spasm of these vessels induced by the irritation of the gas. Animal experiments indicate that air introduced into the coronary circulation, either directly or by injection into the pulmonary vein or left auricle, produces ischemia of the myocardium in areas supplied by involved vessels. The ischemia is demonstrable grossly and by electrocardiographic examination. It may be very temporary, with speedy recovery, or it may persist even after the apparent

complete disappearance of the gas bubbles. Death from ventricular fibrillation may result within a very short time after the injection of the air.

The distribution of air within the arterial circulation is determined by the principle of air buoyancy. This principle may be made use of in the therapy of arterial air embolism.

REFERENCES

1. Durant, T. M., Long, J., and Oppenheimer, M. J.: Pulmonary (Venous) Air Embolism, *AM. HEART J.* 33:269, 1947.
2. Brandes, M.: Ein Todesfall durch Emboli nach Injektion von Wismut Salbe in eine Empyemafistel, *München med. Wchnschr.* 59:2392, 1912.
3. Brauer, L.: Weitere klinische und experimentelle Erfahrungen über arterielle Luftemboli, *Verhandl. d. Deutsch. Gesellsch. f. inn. Med.* 30:347, 1913.
4. Gunderman, W.: Ueber Luftembolie, *Mitt. a. d. Grenzgeb. d. Med. u. Cir.* 33:261, 1921.
5. Leon-Kindberg, M.: Mort subite consecutive a un punction pleurale, *Presse méd.* 10:151, 1925.
6. Olmer, D., and Turries: Les Accidents nerveux graves du pneumothorax artificiel, *Presse méd.* 66:1111, 1925.
7. Cocke, C. H.: Pleural Shock: Report of Four Cases, *Am. Rev. Tuberc.* 24:545, 1931.
8. McKnight, J. B., Gammons, H. F., and Knowles, W. M.: A Case of Pleural Shock, *Am. Rev. Tuberc.* 2:96, 1918.
9. Vandriessche, A.: Les Accidents nerveux subits au cours des insufflations du pneumothorax artificiel, *Rev. belge tuberc.* 17:95, 1926.
10. Capps, J. A., and Lewis, D. D.: Observations Upon Certain Blood-Pressure-Lowering Reflexes That Arise from Irritation of the Inflamed Pleura, *Am. J. M. Sc.* 134:868, 1907.
11. Capps, J. A.: Air Embolism Versus Pleural Reflex as the Cause of Pleural Shock, *J. A. M. A.* 109:852, 1937.
12. Schattenberg, H. J., and Ziskind, J.: Air Embolism as a Complication of Artificial Pneumothorax, *Am. J. Clin. Path.* 9:477, 1939.
13. Dagelish, P. H.: Two Cases of Air Embolism, *Brit. M. J.* 2:256, 1945.
14. Wong, R. T.: Air Emboli in the Retinal Arteries. Report of a Case, *Arch. Ophth.* 25:149, 1941.
15. Reyer, G. W., and Kohl, H. W.: Air Embolism Complicating Thoracic Surgery, *J. A. M. A.* 87:1626, 1926.
16. Wever, E.: Cerebrale Luftembolie, *Beitr. z. Klin. d. Tuberk.* 31:159, 1914.
17. Chase, W. H.: Anatomical and Experimental Observations on Air Embolism, *Surg., Gynec., & Obst.* 59:569, 1934.
18. Schlaepfer, K.: Air Embolism Following Various Diagnostic or Therapeutic Procedures in Diseases of Pleura and Lung, *Bull. Johns Hopkins Hosp.* 33:321, 1922.
19. Rukstinat, G.: Experimental Air Embolism of Coronary Arteries, *J. A. M. A.* 96:26, 1931.
20. Van Allen, C. M., and Hrdina, L. S.: Air Embolism From the Pulmonary Vein. A Clinical and Experimental Study, *Arch. Surg.* 19:567, 1929.
21. Helper, T. K., Truter, J. L., and Hunt, H. F.: Air Embolism Occurring During Mastectomy: Report of a Fatal Case, *Am. J. Clin. Path.* 17:322, 1947.
22. Thomassen, K.: Paradoxical Air Embolism; Case, *Norsk mag. f. laegevidensk* 99:470, 1938.
23. Deadman, W. J.: Fatal Air Embolism; Case Reports, *Canad. M. A. J.* 37:157, 1937.
24. Weyrauch, H. M., Jr.: Death From Air Embolism Following Perirenal Insufflation, *J. A. M. A.* 114:652, 1940.
25. Mylks, G. W., Brown, A. B., and Robinson, C. N.: Air Embolism During Labor, *Canad. M. A. J.* 56:427, 1947.
26. Warring, F. C., Jr., and Thomas, R. M.: Spontaneous Air Embolism Observed in a Case of Pneumoperitoneum, *Am. Rev. Tuberc.* 42:682, 1940.
27. Bohorloush, J. G.: Air Embolism. An Alternate Concept of Its Origin in Pneumothorax, *Am. Rev. Tuberc.* 47:263, 1943.
28. Kelly, H. G., Gibson, W. C., and Meakins, J. F.: Cerebral Air Embolism Following Artificial Pneumothorax; Treatment With Prolonged Inhalation of Oxygen, *Canad. M. A. J.* 5:388, 1947.
29. Liebermeister, G.: Anamisches Zungenphänomen, ein Frühsymptom der Arteriellen Luftembolie, *Klin. Wchnschr.* 8:21, 1929.
30. Smith, A. W.: Case Exhibiting Liebermeister's Syndrome Following on Air Filling of Left Pleural Cavity, *Tubercle* 16:454, 1935.
31. Rukstinat, G., and LeCount, E. R.: Air in Coronary Arteries, *J. A. M. A.* 91:1776, 1928.

32. Moore, R. M., and Braselton, C. W., Jr.: Injection of Air and Carbon Dioxide Into the Pulmonary Vein, *Ann. Surg.* 112:212, 1940.
33. Moore, R. M., and Braselton, C. W., Jr.: Experimental Study of Embolic Effects of Air and of Carbon Dioxide, *South. Surgeon* 9:733, 1940.
34. Kent, E. M., and Blades, B.: Experimental Observations Upon Certain Intracranial Complications of Particular Interest to the Thoracic Surgeon, *J. Thoracic Surg.* 11:434, 1942.
35. Jackson, C., and Babcock, W. W.: Coronary Air Embolism, *S. Clin. North America* 10:1265, 1930.
36. Pollak, M.: Air Embolus, *Am. Rev. Tuberc.* 28:187, 1933.
37. Hall, W. E. B.: Left Heart Arterial Air Embolism: Report of a Case Following Pneumothorax, *J. A. M. A.* 109:125, 1937.
38. Bratkov, B. N., and Verdnikova, P.: Myocardial Infarct as a Sequence of Gaseous Embolism in Artificial Pneumothorax, *Probl. tuberk.* No. 11, 81, 1939.
39. Farr: Quoted by Bratkov and Verdnikova,³⁸ *Arch. pathol. anatomy and pathol. physiology*, Vol. 1, 1935.
40. Durant, T. M.: The Occurrence of Coronary Air Embolism in Artificial Pneumothorax *Ann. Int. Med.* 8:1625, 1935.
41. Cameron, D. R.: Transient Heart Block and Coronary Occlusion in Pleural Shock, *Brit Heart J.* 7:104, 1945.
42. Pruitt, R. D., and Valencia, F.: The Immediate Electrocardiographic Effects of Circumscribed Myocardial Injuries: An Experimental Study, *AM. HEART J.* 35:161, 1948.
43. Dressler, W., and Roesler, H.: High T Waves in the Earliest Stage of Myocardial Infarction, *AM. HEART J.* 34:627, 1947.
44. Fine, J., Frehling, S., and Starr, A.: Experimental Observations on the Effect of 95 Per Cent Oxygen on the Absorption of Air From the Body Tissues, *J. Thoracic Surg.* 7:635, 1935.
45. Fine, J., and Fischmann, J.: An Experimental Study of the Treatment of Air Embolism *New England J. Med.* 223:1054, 1940.
46. Behnke, A. R.: Physiologic and Medical Aspects of Aviation and Deep Sea Diving, *Advances in Internal Medicine*, New York, 1947, Interscience Publishers, Inc., p. 293.
47. Durant, T. M., Long, J. Oppenheimer, M. J., and Wester, M. R.: Effect of Carbon Dioxide and Other Gases on Electrocardiogram of the Right Ventricle, *Proc. Soc. Exper Biol. & Med.* 66:479, 1947.

IDIOPATHIC INFANTILE HYPERPLASTIC AND HYPERTROPHIC CARDIOMEGALY (CONGENITAL CARDIAC HYPERTROPHY)

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THE cause of "congenital idiopathic hypertrophy" of the infantile heart remains an enigma in those cases in which all factors known to produce cardiac hypertrophy have been ruled out.¹ The two mechanisms of idiopathic enlargement which have been suggested are hypertrophy and hyperplasia. Among the studies supporting the thesis of hypertrophy are those of Dammin and Moore,² who demonstrated in their case an increase in the width and total number of fibers without a concomitant increase in the total number of nuclei. The protagonist of hyperplasia as a cause of cardiac enlargement is MacMahon,³ who observed many mitotic figures in the myocardium of a 6-month-old infant whose heart was twice normal weight. The purpose of this article is to present further evidence that idiopathic cardiac enlargement in infants may be the result of myocardial hyperplasia as well as of hypertrophy.

In the hypertrophied adult heart, Karsner, Saphir, and Todd⁴ demonstrated that, while the myocytes and nuclei are not increased in number, the individual fibers are enlarged. Thus, for a given unit of tissue there is a decrease in the number of nuclei because of the increased volume of sarcoplasm, the total number of nuclei in the heart remaining essentially unchanged. Dammin and Moore concluded from a study of their single case of infantile idiopathic myocardial enlargement and a control that, while the total number of nuclei in the heart remains constant, the number and width of the fibers are increased. They felt that their case should be regarded as one of cardiac hypertrophy. Inherent in the previously mentioned criteria for myocardial hypertrophy is a definition of hyperplasia, namely, the demonstration of a significant increase in the total number of myocytes within a given heart.

MATERIALS AND METHODS

The number of nuclei within a high-power field of 0.35 mm. diameter and calculated to be 0.00058 c.mm. in volume was counted in a total of seventeen hearts from subjects varying in age from 5½ months' gestation to 4 years (Table I). Three of these cases represent instances of idiopathic cardiac enlargement. In all the subjects the material examined was obtained from the left ventricle; it was fixed in Helly's modification of Zenker's fluid, and cut 6.0 microns in thickness. The tissues were processed uniformly and stained with hematoxylin and eosin to avoid variations in shrinkage peculiar to different methods.

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TABLE I. SUMMARY OF THE FINDINGS IN SEVENTEEN INFANTS VARYING IN AGE FROM 5½ MONTHS GESTATION TO 4 YEARS

CASE NUMBER (AUTOPSY NUMBER)	AGE* (MONTHS)	SEX	BODY WEIGHT (GRAMS)	HEART WEIGHT (GRAMS)	NORMAL HEART WEIGHT ⁵ (GRAMS)	NUCLEI IN 0.00058 C.MM. OF MYOCARDIUM	CAUSE OF DEATH
1. 5074	5.5 g	F	765	5		468	Prematurity
2. 5096	6.0 g	F	870	9		569	Prematurity
3. 5235†	6.25g	M	1,400	10		758	Prematurity
4. 5258	7.5 g	F	1,350	11		514	Prematurity
5. 5159	9.0 g	M	3,320	18	17	504	Respiratory failure
6. 491†	2.5	F	3,700	55	23	436	Myocardial hyperplasia
7. 5242	2.75	M	3,130	24	23	449	Atresia of jejunum
8. 4369	3.0	M	4,520	25	23	456	Pneumonia
9. 4149	3.25	F	3,000	18	23	377	Acidosis and pneumonia
10. 5202†	4.0	F	7,060	43	27	251	Pneumonia
11. 5180†	4.0	M	4,555	73	27	390	Diarrhea; acidosis
12. 5140	4.5	F	4,200	35	27	365	Cystic fibrosis of pancreas
13. 4114	4.5	F	4,000	30	27	398	Pneumonia
14. 4252	5.0	M	6,290	30	29	449	Pneumonia; meningitis
15. 5185	5.5	M	7,850	35	29	362	Letterer-Siwe's disease
16. 5245	12.0	M	Unknown	42	44	310	Kernicterus
17. 5171	48.0	M	14,700	.80	73	226	Polar spongioblastoma

*g = months of gestation.

†Reported cases.

The counting field was divided into sixteen parts. These, after being tallied individually, were totaled. Five such groups were averaged for each normal heart and ten for the three enlarged hearts. The normal hearts were so small that usually not more than five fields could be found free of large vessels and artefacts in any given section. Approximately 25 per cent of the identical fields were counted by an associate without the knowledge of the authors' results. The discrepancy between the two totals never exceeded 5.4 per cent.

REPORT OF CASES

CASE 11 (Autopsy 5180).—This is the case of a 4-month-old Negro male infant who had been delivered at full term without complications. At 1½ months of age while being changed from breast feedings to a formula, he developed diarrhea, which continued until death. In his third month of life he suffered an upper respiratory infection complicated by otitis media, which clinically was believed to have resolved. Death was preceded by dyspnea, stupor, and cyanosis. The carbon-dioxide combining power was reduced to 15 volumes per cent and respirations became grunting just prior to death.

At autopsy the body weighed 4,555 grams. There was moderate dehydration and loss of subcutaneous fat. The heart weighed 73 grams (normal weight, 27 grams). Both ventricles were dilated and thickened, and the left ventricle midway between the base and apex measured 1.0 cm. in thickness. The ductus arteriosus was closed. The foramen ovale was functionally closed but anatomically patent; that is, the valves overlapped. Valvular defects and anomalous vessels were not found. There was no aortic coarctation. Microscopic study (Fig. 1) revealed myocardium showing no scarring or degeneration but with more than the usual number of nuclei. Mitotic figures were not seen after careful search. Glycogen stains were negative. Fat stains revealed small numbers of tiny colloidal droplets of fat within the sarcoplasm. The lungs showed minimal intra-alveolar edema with focal areas of atelectasis. The liver showed moderate fatty degeneration without passive congestion. The spleen and pancreas did not present lesions. The

renal tubular epithelium revealed acute parenchymatous degeneration. There were no glomerular or arterial lesions in the kidney. A right subacute mastoiditis with chronic abscess formation was the cause of parenteral diarrhea resulting in acidosis and death. The final diagnoses were myocardial hyperplasia and enlargement, right subacute suppurative mastoiditis, and pulmonary edema.

CASE 6 (Autopsy 491).—This 2½-month-old white female infant was born prematurely after eight months of gestation without complications. Her birth weight was 2,170 grams. Development was normal except for occasional episodes of cyanosis. On her last day of life the infant vomited and became cyanotic without evidence of aspiration of vomitus. Radiologic examination revealed a markedly enlarged heart. Despite therapy the child developed convulsions and died.

At autopsy the body weighed 3,700 grams. The heart weighed 55 grams, and its foramen ovale was probe patent. The valves were not unusual; the left ventricle measured 7.0 mm. and the right, 3.0 mm. in thickness. The ductus arteriosus was closed. The aorta showed no coarctation. Microscopic study (Fig. 1) showed a marked increase in the number of cardiac nuclei lying within fibers whose diameters were no greater than those of the nuclei. There was no evidence of degeneration or scarring. The vacuolization characteristic of excessive glycogen or fat storage was absent. The lungs were atelectatic in some areas. Other than those, no noteworthy lesions were discovered either in the kidneys or elsewhere. The final diagnoses were myocardial hyperplasia with cardiac enlargement and focal pulmonary atelectasis.

CASE 10 (Autopsy 5202).—This 4-month-old Negro female infant had been delivered at full term without complications. At 3 months of age she developed a mild rhinitis which persisted until her death. She was found comatose in bed one morning without any prodrome other than the mild rhinitis. The temperature was 30° centigrade. Numerous crackling râles were heard over the chest, and death followed within three hours.

At autopsy the well-nourished and well-developed infant weighed 7,060 grams. The heart weighed 43 grams. The ductus arteriosus and foramen ovale were closed. The coronary arteries were not unusual. The aortic circumference at its narrowest point, the entrance of the ductus, was 2.7 centimeters. Valvular defects were not found. Microscopic study (Fig. 1) revealed a relative increase in the sarcoplasm-nuclear ratio. There were no vacuoles within the sarcoplasm. Fat stains revealed no abnormality; glycogen stains were not made. One lung weighed 65 grams and the other, 70 grams; both showed an acute, diffuse, interstitial pneumonia. Alpha streptococcus and hemolytic staphylococcus were cultured from the lungs. The larynx was acutely inflamed. The liver weighed 350 grams and showed minimal fatty and acute parenchymatous degeneration. The spleen, pancreas, and adrenal glands showed no lesions. The kidneys revealed no evidence of glomerular or arterial disease; however, the tubular epithelium showed cloudy swelling. The acute bilateral interstitial pneumonia was considered the cause of death. The final diagnoses were myocardial hypertrophy and acute bilateral interstitial pneumonia.

CASE 3 (Autopsy 5235).—This Negro male infant was the second of twins delivered without complications after six and one-fourth months of gestation. He expired after twenty-eight hours of life, never having developed normal respirations. At autopsy the infant weighed 1,400 grams and measured 40 cm. from crown to heel. The heart, which was not enlarged, weighed 10 grams. Both ductus and foramen ovale were patent. Neither congenital anomalies of the heart nor valvular lesions were demonstrable. The aorta was normal throughout. Histologic study of the myocardium (Fig. 1) revealed a syncytium containing an unusually large number of nuclei. There was no degeneration, fibrosis, or vacuolization such as is encountered in excessive glycogen or fat storage. The lungs were atelectatic and congested. Much hematopoiesis was seen within the liver and spleen. The neogenetic zone of the kidneys was prominent, but no lesions were recognized. The adrenal glands showed autolysis. The cerebral ventricles contained blood-tinged fluid with no concomitant brain lacerations. The final diagnoses were myocardial hyperplasia without enlargement, moderate intraventricular cerebral hemorrhage, and focal pulmonary atelectasis.

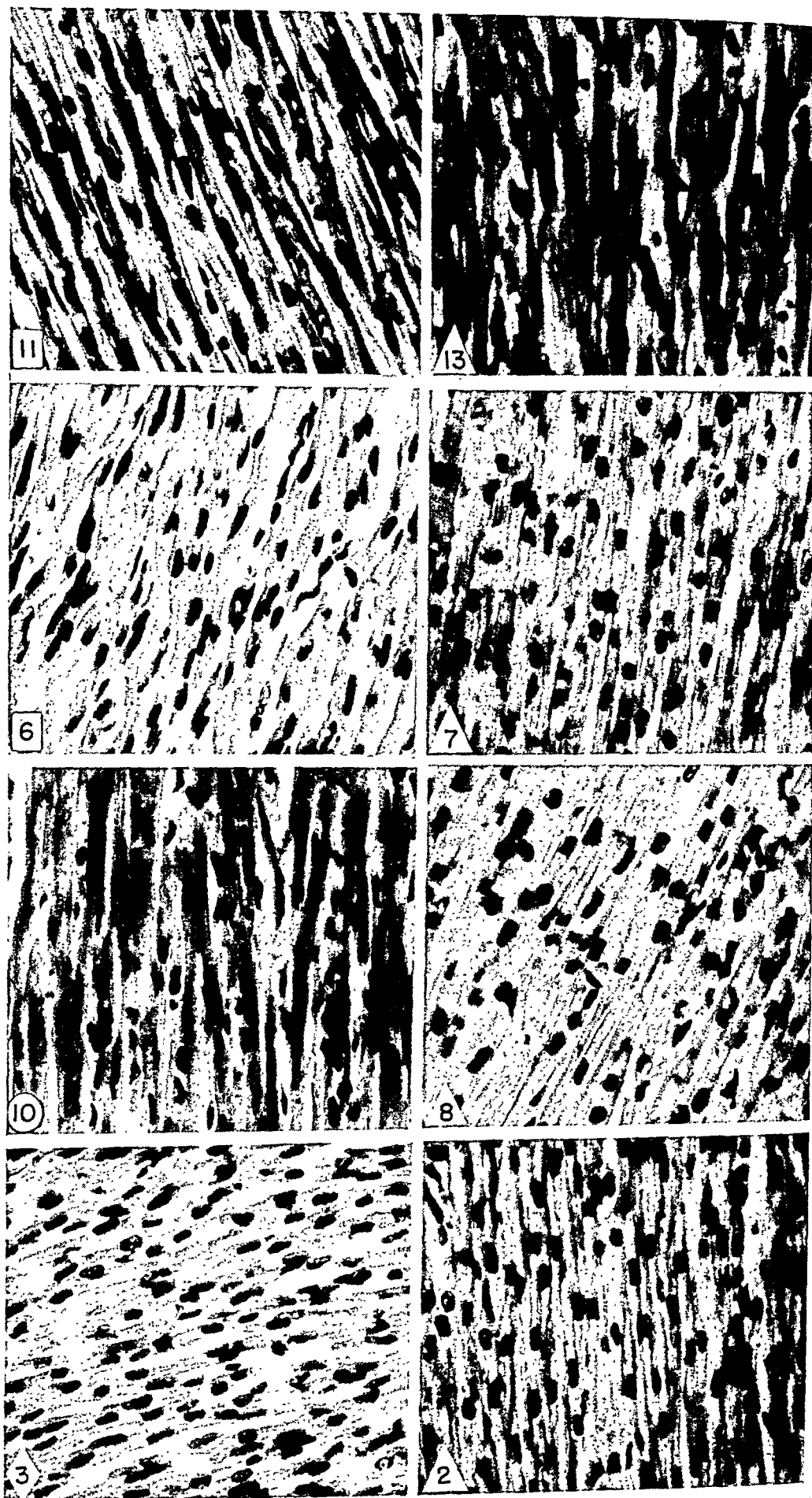


Fig. 1.—Hyperplastic and hypertrophic hearts on left, control hearts on right. □ Hyperplastic cardiomegaly; ○ hypertrophic cardiomegaly; ◇ hyperplasia with normal mass; △ control.

DISCUSSION

The data of the seventeen cases are tabulated in Table I. A perusal of the heart weights reveals that in Patients 6, 10, and 11 the hearts are obviously enlarged since the smallest of the three (Case 10) weighs 59 per cent more than the average heart of an infant of the same age. The hearts of Patients 6 and 11 are even more strikingly enlarged, being, respectively, 139 and 170 per cent heavier than their estimated normal weights.

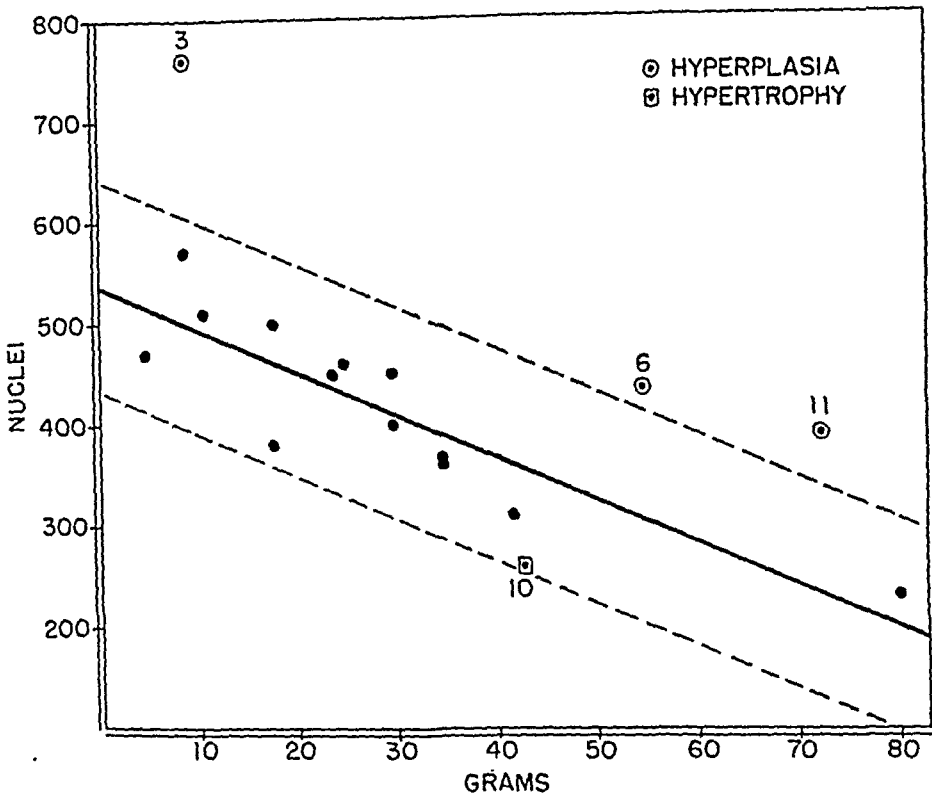


Fig. 2.—Scatter diagram showing number of myocyte nuclei in 0.00058 c.mm. of each of seventeen hearts correlated with total cardiac mass. The continuous line is the mean of the values. The dotted lines enclose an area of two and one-half σ above and below the mean.

In contrast to the normal heart of an infant of the same age (4 months), Patient 10 shows a paucity of nuclei within any given microscopic field. This observation led to the conclusion that enlargement of the heart was a consequence of an increase in the size of its individual myocytes; in short, hypertrophy. In order to establish this diagnosis, the myocardial nuclei of several normal hearts of infants of approximately the same age were counted and their number compared with that of Patient 10. Table I shows that at 3 months of age one infant possessed 456 nuclei per 0.00058 c.mm. of heart. At 4.5 months two infants showed, respectively, counts of 365 and 398 per 0.00058 c.mm. The heart of Patient 10, in contrast, has only 251 nuclei within the same volume of tissue. Despite this, it weighed 59 per cent more than the normal weight of 27 grams.

METHOD OF STUDY

Two patients who were experiencing transient seizures of ventricular fibrillation and two patients with periodic standstill of the ventricles form the subjects of this study. In one patient recurring attacks of transient ventricular fibrillation appeared after the development of transient periods of A-V dissociation in the course of a normal sinus mechanism. The other three patients had established A-V dissociation.

These experiments were carried out at a time when it was certain that the patients had not had any changes in their cardiac mechanism for at least forty-eight hours. It was definitely determined from both a study of the heart and pulse rates, while the patients were connected to the electrocardiographic circuit, that the basic ventricular rate was fairly constant prior to the onset of the experiments, that is, that it did not vary more than five beats per minute. Two patients were in bed constantly and two were ambulatory. No drugs were administered for at least one week prior to these studies. All four patients had mild signs of congestive heart failure with shortness of breath and three had cyanosis of the lips and nail beds.

One method of rebreathing was identical to that used by others in similar experiments.¹⁵ The subject was placed in a reclining position and connected to a basal metabolism machine filled with room air and the carbon dioxide was removed by soda lime. Another method consisted of having the subject rebreathe in a small canvas bag filled with room air without the removal of the carbon dioxide. Continuous electrocardiograms were recorded prior to, during, and subsequent to the rebreathing periods.

The experiments were terminated when such signs were observed as loss of mental attention and sustained voluntary control, intense cyanosis, or abnormal changes in the type of breathing.

RESULTS

The Effects of Anoxemia on Patients With Transient Ventricular Fibrillation.—One woman showed a sinus rhythm and developed transient seizures of ventricular fibrillation after the onset of A-V dissociation. Rebreathing for only four minutes and thirty-seven seconds changed her sinus mechanism to one of heart block with the auricles beating 78 per minute and the ventricles 32. This type of A-V dissociation persisted after the termination of the experiment for several days before there was a return to the sinus mechanism. It is of interest to note that the heart block could also be readily induced in this patient by the intramuscular injection of epinephrine hydrochloride¹⁶ as well as by the intravenous injection of digitalis bodies.¹⁷

In this woman and in another patient the effects of rebreathing were variable when the A-V dissociation had already been established. In the first case, rebreathing either in the basal metabolism machine or in the bag yielded no change in the cardiac rhythm except a slight acceleration of the auricles at the end of seventeen minutes when the experiment had to be discontinued because of discomfort. The ventricular rate remained unchanged.

to the abscissa, should, for its weight, have approximately 305 nuclei per unit volume instead of its actual count of 436. When the point occupied by the heart of Patient 6 is extended to the ordinate, it falls on a locus corresponding to a heart weight of 24 grams. This weight is normal for a heart with a count of 435 nuclei per unit volume and corresponds to the expected weight for a normal individual of the age of Patient 6. This, then, indicates that the cause of the enlargement is an increase in the total number of normal-sized myocytes. The same conclusion may be drawn from Fig. 1 for the heart of Patient 11.

Fig. 2 illustrates the number of nuclei in a given volume of myocardium correlated with the age of the individuals. It is apparent that the two hyperplastically enlarged hearts lie within the areas of the normal, thus again re-emphasizing the conclusion that the individual myocytes are of normal size and that the cardiomegaly is due to hyperplasia of its units. In contrast to these, the heart of Patient 10, the hypertrophic organ, lies well outside the "normal" curve, indicating that it contains far fewer nuclei per unit volume of normal myocardium of its age group and that its larger mass is due to an increase in the size of each element; in short, hypertrophy.

The heart of Patient 3 presents interesting possibilities. It shows no increase in mass; however, the fact that it contains more nuclei per unit volume than its controls, the hearts of Patients 2 and 4 (Table I), indicates that hyperplasia is present. Whether such an organ in the natural course of its development might give rise to an enlarged hyperplastic heart by virtue of increase in size of its individual myocytes cannot be predicted. Nonetheless, the possibility is less than remote, and may indicate that, in contrast to hypertrophic cardiomegaly, hyperplastic cardiomegaly is a developmental anomaly. The former in its mechanism of adaptation follows the pattern of the adult heart, namely, hypertrophy. The nature of the initiating stimulus is unknown, a fact which places these cases in the same category with Christian's⁶ nonhypertensive chronic nonvalvular heart disease, and represents, as in the adult, an acquired lesion.

MacMahon³ found mitoses in his case of hyperplastic cardiomegaly. None could be found in the two examples of this report.

SUMMARY AND CONCLUSIONS

1. It is concluded from a study of three enlarged infantile hearts that the mechanism of hypertrophy or of hyperplasia may be responsible for the production of so-called "congenital idiopathic cardiac hypertrophy."
2. Because of the fundamental difference between the two processes, it is suggested that a differential terminology be adopted: infantile hypertrophic cardiomegaly and infantile hyperplastic cardiomegaly.
3. Definitive conclusions regarding the cause of the two mechanisms of cardiac enlargement cannot be drawn from the data presented. However, the suggestion is made that hyperplastic cardiomegaly may be a developmental anomaly and hypertrophic cardiomegaly an acquired lesion.

REFERENCES

1. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children, *Am. J. Dis. Child.* 45:828, 1933.
2. Dammin, G. J., and Moore, R. A.: Cardiac Muscle in Idiopathic Hypertrophy of the Heart in Infancy and in Normal Growth, *Arch. Path.* 27:122, 1939.
3. MacMahon, H. E.: Hypertrophy of Heart in Infants, *Am. J. Dis. Child.* 55:93, 1933.
4. Karsner, H. T., Saphir, O., and Todd, T. W.: Cardiac Muscle in Hypertrophy and Atrophy, *Am. J. Path.* 1:351, 1925.
5. Coppoletta, J. M., and Wolbach, S. B.: Body Length and Organ Weights of Infants and Children, *Am. J. Path.* 9:55, 1933.
6. Christian, H. A.: *The Principles and Practice of Medicine*, ed. 16, New York, 1937, D. Appleton-Century Company, p. 1030.

Stein, I. D., Harpuder, K., and Byer, J.: Effect of Sympathectomy on Blood Flow in the Human Limb. *Am. J. Physiol.* 152:499 (March), 1948.

Plethysmographic studies in a small group of patients with various peripheral vascular diseases (thromboangiitis obliterans, arteriosclerosis, Raynaud's syndrome, cold injury, and essential hypertension) confirmed previous observations that sympathectomy fails to increase the resting blood flow within muscles, but does increase the skin circulation of the denervated extremity. The calf was used to test predominantly muscle blood flow, while the flow in the foot represented primarily skin circulation. Blood flow in muscles could be effectively increased by exercise, tissue heating, or release of temporary arterial occlusion. These procedures are known to release vasodilating metabolites. It is implied that sympathectomy will be useful clinically only for lesions or symptoms resulting primarily from deficient skin circulation.

HECHT.

Eckenhoff, J. F., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of Hypotension on Coronary Blood Flow, Cardiac Work, and Cardiac Efficiency. *Am. J. Physiol.* 152:545 (March), 1948.

Hypotension was produced by the subdural injection of procaine hydrochloride or by the intravenous injection of tetraethyl ammonium chloride in anesthetized dogs whose coronary blood flow was being measured by the nitrous oxide method. Cardiac work and efficiency were calculated from venous catheterization data.

Diminished cardiac output with marked reduction in cardiac work accompanied the fall in blood pressure in seven of the eight experiments. Coronary blood flow declined in all instances (average, 25 per cent) but relatively less than cardiac work, which on the average fell 56 per cent. Cardiac efficiency, which is the work done divided by energy intake, declined 36 per cent. This would appear to indicate a decreased capacity of the heart to perform its work under these conditions, but evidence for such capacity is lacking, since the hypotension did not seem to be harmful to the experimental animal. The discrepancy is thought to lie in the concept of mechanical cardiac efficiency, the calculation of which fails to include the utilization of oxygen for factors other than actual mechanical work, such as the energy used for the maintenance of the cardiac muscle cells, or that required for isometric ventricular contraction. Cardiac efficiency, as calculated, is not a valid criterion of the heart's capacity for work under changing experimental conditions.

HECHT.

Galdston, M., and Steele, J. M.: Arterial Pressure Waves in a Patient With Coarctation of the Aorta. *Am. J. Physiol.* 152:554 (March), 1948.

In addition to recording the usual arterial pressure pulse waves in an upper and lower extremity in a patient with coarctation of the aorta, the arterial tracing from a collateral artery connecting the arterial tree above and below the coarctation was recorded by the means of a Hamilton intra-arterial manometer. The pressure in the collateral vessel, the left subscapular artery, whose lumen measured 0.5 cm. in diameter, was 215/100. The pressure and the form of the pulse tracing were identical to those of the left radial artery although the collateral artery arose distal to the obstruction. The coarctation and the anatomical arrangement of the collateral circulation were confirmed by autopsy.

HECHT.

Lenel, R., Katz, L. N., and Rodbard, S.: Arterial Hypertension in the Chicken. *Am. J. Physiol.* 152:557 (March), 1948.

Hypertension was consistently produced in chickens when saline solution was substituted for drinking water. After sixty days of saline intake the average systolic and diastolic pressures rose from the control average of 132/117 to an average of 182/154. Prompt fall in blood pressure followed withdrawal of the saline. The degree of hypertension was further increased by raising

RESULTS

Extraction of Renin Added to Plasma.—Two series of experiments of this type were carried out, indicating both the recovery of added renin and the absence of hypertensinase. Table I contains the pertinent figures of one of these series.

TABLE I. RECOVERY OF RENIN ADDED TO NORMAL DOG PLASMA

EXPERIMENT NUMBER	SWINGLE UNITS OF RENIN ADDED	INCUBATION TIME (MINUTES)	TEST ANIMAL	BLOOD PRESSURE RISE (MM. HG)
1	1/4	10	Dog	42
	1/2	10		70
	1*	10		38
	2	10		76
2	1/6	60	Dog	48
	1/9	60		47
	1/12	60		50
	0 (Control)	60		0.0
3	1/33	30	Dog	43
	1/33	120		40
	1/33	240		40

In this sample only one-half of the total hypertensin yield was used in the bio-assay.

Fig. 1 is a reproduction of the kymographic record obtained in Experiment 1. As can be seen in Experiment 1, hypertensin formation is not dependent on the renin amount when relatively large quantities of renin are used, such as 1/2, 1, and 2 Swingle units. This has been reported previously.⁶ For longer incubation times as applied in Experiment 2, even 1/12, 1/9, and 1/6 unit represent relatively large renin amounts; in consequence, the hypertensin yield is practically identical.

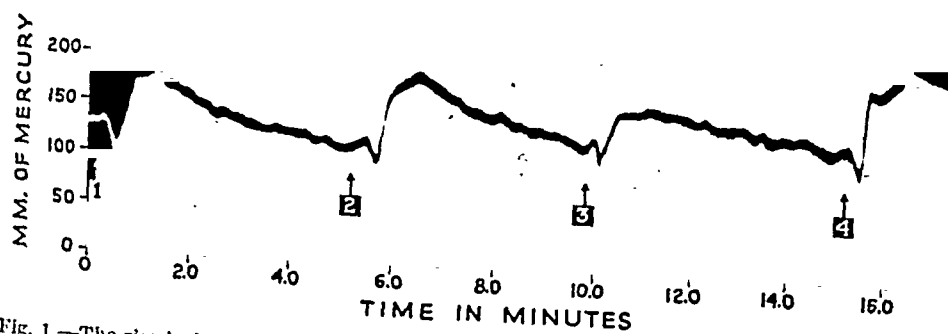


Fig. 1.—The rise in blood pressure following the intravenous injection, into a dog, of hypertensin formed on incubation of different amounts of renin with hypertensinogen: 1, 1/4 unit (Swingle) of renin; 2, 1/2 unit of renin; 3, 1 unit of renin *; and 4, 2 units of renin.

*Only one-half of the total hypertensin yield was injected.

Special attention is directed to Experiment 3 of Table I. The unchanged amount of hypertensin after thirty minutes, two hours, and four hours of incubation is sufficient evidence for the absence of hypertensinase.

The problem of whether significant amounts of hypertensinase are soluble in 40 per cent saturated ammonium sulfate solution was studied in two separate sets of experiments. Freshly prepared scrapings of intestinal mucosa of a dog known to be rich in hypertensinase¹¹ were lyophilized and extracted for one-half hour with 40 per cent saturated ammonium sulfate solution. The extract was centrifuged, the supernatant fluid dialyzed until free of salt and incubated for four hours with known amounts of hypertensin. The solution was then deproteinized, the filtrate lyophilized, and the residue redissolved and tested in a dog. The pressure effect of the equivalent amounts of nonincubated and incubated hypertensin was the same, indicating that no appreciable amounts of hypertensinase had been extracted from the intestinal mucosa.

Sensitivity of the Extraction Method for Renin.—The sensitivity of the method was tested in two series of experiments in which 1/100, 1/200, and 1/300 Swingle unit of hog renin were added to 20-c.c. samples of dog plasma. The latter were then lyophilized and treated as described. The results of these two experiments were similar; the outcome of one is described in Table II and in Fig. 2.

TABLE II. RECOVERY OF SMALL AMOUNTS OF RENIN ADDED TO NORMAL DOG PLASMA

EXPERIMENT NUMBER	SWINGLE UNITS OF RENIN ADDED	INCUBATION TIME (MINUTES)	TEST ANIMAL	BLOOD PRESSURE RISE (MM. HG)
4	1/100 1/200 1/300	240	Cat	40 28 14

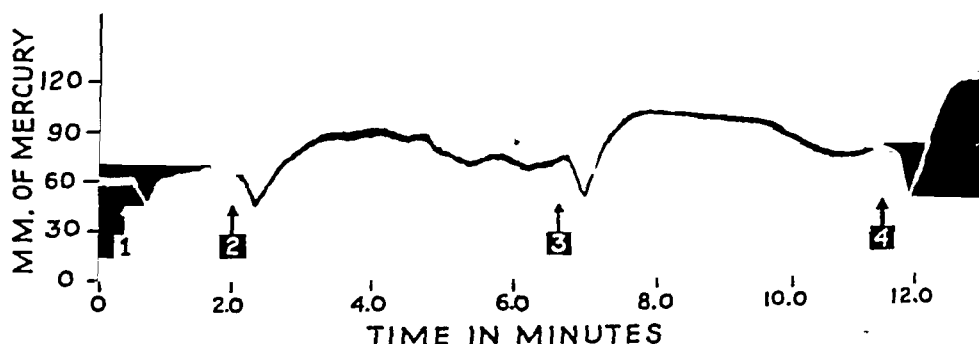


Fig. 2.—The rise in blood pressure following the intravenous injection, into a cat, of hypertensin formed on incubation of different amounts of renin with hypertensinogen: 1, Control (no renin); 2, 1/300 unit (Swingle) of renin; 3, 1/200 unit of renin; and 4, 1/100 unit of renin.

As can be seen, a renin amount of 1/300 of a unit in 20 c.c. of plasma was detectable in a bio-assay on this particularly large cat (weight, 3.6 kilograms). In a second experiment with a test cat of 1.9 kilograms, the hypertensin formed from 1/300 of a unit of renin elevated the blood pressure 41 millimeters. It is very probable, therefore, that 1/400 to 1/500 Swingle unit of renin in 20 c.c. of plasma can be detected.

*Application of the Method to the study of Plasmas of Hypertensive Patients.**—Pertinent data referring to the plasma of fifteen hypertensive patients who had no past history of renal disease follow.

CASE 1.—Blood pressure, 270/130. Renin in plasma: 0. The patient was a 75-year-old white man who had had known hypertension for three years. The fundi showed blurring of the discs and two small, shiny, white patches. Death occurred from left ventricular failure one week after blood sample was taken. Autopsy showed generalized arteriosclerosis. The kidneys showed advanced arterio- and arteriolosclerosis, with hyalinization of many glomeruli and tubules.

CASE 2.—Blood pressure, 220/120. Renin in plasma: 0. The patient was a 56-year-old white man who had had known hypertension and diabetes for three years. Cardiac decompensation began in 1947. The nonprotein nitrogen was 117 mg. per cent. Urine examination showed a 4-plus albumin and granular casts.

CASE 3.—Blood pressure, 190 to 230/120 to 130. Renin in plasma: 0. The patient was a 54-year-old white woman who had had known hypertension and diabetes for four years. The nonprotein nitrogen was 26 mg. per cent. There was hypertensive retinopathy.

CASE 4.—Blood pressure, 225 to 250/120 to 135. Renin in plasma: 0. The patient was a 51-year-old white woman with known hypertension for one and one-half years. The fundi showed small hemorrhages, with obliteration of both discs.

CASE 5.—Blood pressure, 220/140. Renin in plasma: 0. The patient was a 56-year-old white woman who had had known hypertension and diabetes for two years. She had a cerebral vascular accident and developed pyelitis. The nonprotein nitrogen was 40 to 50 mg. per cent. Urine examination showed no casts, no red cells, and many white cells.

CASE 6.—Blood pressure 230/120. Renin in plasma: 0. The patient was a 72-year-old white man who had had known hypertension for twenty years. The fundi showed arteriovenous nicking, with many old linear scars and pigmentations, and scattered flame-shaped hemorrhages. The nonprotein nitrogen was 44 mg. per cent. Urine examination showed no albumin, no red cells, and a few hyaline casts.

CASE 7.—Blood pressure, 230/125. Renin in plasma: 0. The patient was a 50-year-old Negro man who had had known hypertension for four years. The fundi were not visible because of cataract. There was a slight cerebral vascular accident. The nonprotein nitrogen was 31 mg. per cent. The phenolsulfonphthalein test was 65 per cent in four hours. Urine examination showed no red cells and no albumin; the specific gravity was 1.025.

CASE 8.—Blood pressure, 200 to 240/104 to 130. Renin in plasma: 0. The patient was a 70-year-old white woman with known hypertension for twenty years. There was blurring of vision. A cerebral vascular accident occurred. The nonprotein nitrogen was 25 mg. per cent. Urine examination showed no red cells, albumin, or casts.

CASE 9.—Blood pressure, 210/100. Renin in plasma: 0. The patient was an 81-year-old white man who had had known hypertension for five years. There was a slight cardiac decompensation, with a nonprotein nitrogen of 41 mg. per cent. Urine examination showed no red cells, albumin, or casts.

CASE 10.—Blood pressure, 220/115. Renin in plasma: blood pressure elevation of test cat was 20 mm. of mercury. The patient was a 72-year-old white woman who had had known hypertension for five to ten years. The fundi showed normal discs, with marked narrowing and silver-wiring of arteries. There were no hemorrhages or exudates.

CASE 11.—Blood pressure, 220/120. Renin in plasma: 0. The patient was a 61-year-old white woman who had had known hypertension for over twenty years. The nonprotein nitrogen was 35 mg. per cent. The fundi were benign. Urine examination showed a trace of albumin with no red cells and no casts.

*The blood samples were obtained through the courtesy of the Medical and Obstetrical Services affiliated with the Yale School of Medicine.

CASE 12. Blood pressure, 220/120. Renin: 0. The patient was a 57-year-old Negro man who had had known hypertension for nine years. The fundi showed no hemorrhages or exudate. The nonprotein nitrogen was 35 mg. per cent. Urine examination revealed no casts, no red cells, and no albumin.

CASE 13.—Blood pressure, 180/100. Renin: 0. The patient was a 65-year-old white woman who had had known hypertension for two years. The nonprotein nitrogen was 35 mg. per cent. Urine examination showed no casts, red cells, or albumin.

CASE 14.—Blood pressure, 205/105. Renin: 0. The patient was a 71-year-old white man. The duration of hypertension was not known. The fundi were normal. Urine examination showed no red cells, no casts, and no albumin.

CASE 15.—Blood pressure, 250/120. Renin in plasma: blood pressure elevation of test cat was 45 mm. of mercury. The patient had been a known hypertensive for many years. The blood was drawn during serious cardiac decompensation.

The plasma samples of thirteen of the fifteen patients were definitely negative; the two positive samples will be discussed later.

The following three plasma samples were obtained from patients suffering from toxemia of pregnancy.

CASE 16.—Blood pressure, 155/100. Renin in plasma: 0. The patient was a 49-year-old white woman with toxemia of pregnancy. There was a transient slight hypertension, the blood pressure varying from 135/92 to 155/100. The fundi were normal. Urine examination gave a 2 plus to 3 plus test for albumin; no red cells, and no casts were present.

CASE 17.—Blood pressure, 198/110. Renin in plasma: blood pressure elevation of test cat was 14 mm. of mercury. The patient was a 43-year-old white woman with toxemia of pregnancy. The nonprotein nitrogen was 29 mg. per cent. Urine examination gave a 3 plus test for albumin, with no casts. Blood pressure after delivery was 135/76. Recovery was uneventful.

CASE 18.—Blood pressure, 170 to 182/110 to 128. Renin in plasma: 0. The patient was a 25-year-old white woman with toxemia of pregnancy. The nonprotein nitrogen was 31 mg. per cent. Urine examination gave a 2 plus test for albumin, no red cells, and no casts. Blood pressure after delivery was 140/70.

The last three patients had a history of kidney involvement. The test on one (Case 20) was negative, that on another (Case 19) led to a rise in pressure of 11 mm. of mercury. Since repeated control injection with 10 c.c. of saline resulted in blood pressure rises of 8 to 10 mm. Hg, the comparable test rise of 11 mm. was considered insignificant.

CASE 19.—Blood pressure, 230/160. Renin in plasma: blood pressure elevation of test cat 11 mm. of mercury. The patient was a 41-year-old white man. Five years ago he had noted swelling of the face. At that time he had albuminuria and hypertension. In 1947 the patient complained of polyuria and nocturnal dyspnea. In 1948 there was loss of visual acuity. The fundi showed choked discs, with slight papilledema, the arteries were partially obliterated, and there were innumerable scattered fresh and old hemorrhages. He died in left ventricular failure two months after the blood sample was taken. The autopsy findings were those of malignant nephrosclerosis. There were acute arteriolar changes such as necrosis and thrombosis. The surface of the kidneys was granular, with some petechial hemorrhages.

CASE 20.—Blood pressure, 240/120. Renin in plasma: 0. This patient was diagnosed clinically as having chronic glomerulonephritis.

CASE 21.—Blood pressure, 190 to 210/110 to 130. Renin in plasma: blood pressure elevation of test cat was 14 mm. of mercury. The patient was a 55-year-old Negro man who had had hypertension for five years. The fundi showed markedly tortuous vessels with arteriovenous nicking; there were no hemorrhages. There was a cerebral vascular accident. The nonprotein nitrogen was 44 mg. per cent. Urine examination showed slight albumin, no red cells, and many granular casts. The patient died in cardiac failure nine days after the blood sample was taken. Autopsy findings were those of generalized arteriosclerosis with moderately arteriosclerotic kidneys. The glomeruli were swollen and cellular.

DISCUSSION

Hog renin added to freshly prepared dog plasma was extracted with 40 per cent saturated ammonium sulfate solution from the plasma after its lyophilization. This method of extraction of renin and separation from hypertensinase seems to be satisfactory for the enzymatic determination of small renin quantities in large plasma amounts. It was used to reinvestigate the presence of renin in the blood in human cases of hypertension. No trace of renin was found in thirteen plasma samples of a series of fifteen patients with "essential" hypertension. The blood sample of the fourteenth patient, withdrawn when the patient was in acute cardiac failure, indicated the presence of renin. In the light of recent reports¹² describing the occurrence of renin in the blood in cardiac decompensation, this positive result might be ascribed to the passive congestion of the kidney. There was no trace of renin in the plasma samples of two of three patients with toxemia of pregnancy, nor was there any significant renin action in the plasma samples of two of three patients with "renal" hypertension. The two positive samples of the last two series, as well as the one of the first series, were associated with such small hypertensin formation (blood pressure rises of 14, 14, and 20 mm. Hg) that only traces of renin could have been present in the blood. These traces were by far too small to elicit even the slightest pressor effect on direct intravenous injection. The conclusion, therefore, seems warranted that there is no significant relationship between the occurrence of renin and the elevation of blood pressure in human cases of hypertension.

SUMMARY

Renin free of hypertensinase has been extracted from lyophilized plasma by aid of a 40 per cent saturated ammonium sulfate solution. Application of this method to twenty-one patients with hypertension gave seventeen negative, one moderately positive, and three slightly positive results. The moderately positive blood was withdrawn from a patient with acute cardiac decompensation and probably cannot be ascribed to the earlier hypertension. The three slightly positive cases indicate quantities of renin that are much too small to elicit even a minimal pressor effect on intravenous injection.

REFERENCES

1. Braun-Menéndez, E., Fasciolo, J. C., Leloir, L. F., and Muñoz, J. M.: The Substance Causing Renal Hypertension, *J. Physiol.* 98:283, 1940.
2. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting From the Reaction Between Renin and Renin Activator, *J. Exper. Med.* 71:29, 1940.

3. Dexter, L., and Haynes, F. W.: Relation of Renin to Human Hypertension With Particular Reference to Eclampsia, Pre-eclampsia and Acute Glomerulonephritis, *Proc. Soc. Exper. Biol. & Med.* 55:288, 1944.
4. Taquini, A. C., and Fasciolo, J. C.: Renin in Essential Hypertension, *AM. HEART J.* 32:357, 1946.
5. Dexter, L.: Mechanisms of Human Hypertension, *Am. J. Med.* 4:279, 1948.
6. Mylon, E., Lund, M., and Heller, J. H.: Limitations of the Renin Hypertensin Hypothesis, *Am. J. Physiol.* 152:397, 1948.
7. Goldblatt, H.: Renal Origin of Hypertension, *Physiol. Rev.* 27:120, 1947.
8. Leloir, L. F., Muñoz, J. M., Braun-Menéndez, E., and Fasciolo, J. C.: Sécrétion de rénine et formation d'hypertensine, *Rev. soc. argent. de biol.* 16:75, 1940. (Quoted from "Renal Hypertension."¹¹)
9. Leloir, L. F., Muñoz, J. M., Braun-Menéndez, E., and Fasciolo, J. C.: Dosaje de la Renina, *Rev. soc. argent. de biol.* 16:635, 1940. (Quoted from "Renal Hypertension."¹¹)
10. Swingle, W. W., Taylor, A. R., Collings, W. D., and Hays, H. W.: Preparation and Bioassay of Renin, *Am. J. Physiol.* 127:768, 1939.
11. Braun-Menéndez, E., Fasciolo, J. C., Leloir, L. F., Muñoz, J. M., and Taquini, A. C.: "Renal Hypertension," translated by Dexter, L., Springfield, Ill., 1946, Charles C Thomas, Publisher, p. 172.
12. Merrill, A. J., Morrison, J. L., and Brannon, E. S.: Concentration of Renin in Renal Venous Blood in Patients With Chronic Heart Failure, *Am. J. Med.* 1:468, 1946.

THE HEART MUSCLE AND THE ELECTROCARDIOGRAM IN CORONARY DISEASE

I. SURVEY OF STANDARDS AND METHODS FOR OBTAINING THE ANATOMIC DATA REQUISITE FOR CLINICOPATHOLOGIC CORRELATION

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THE aim of this investigation was to answer the question: To what extent is it possible to correlate the electrocardiographic pattern of patients suspected of having coronary disease with myocardial damage demonstrable at the autopsy? To this end we have studied the distribution, size, shape, and probable duration of infarcts and scars in the ventricular walls of a series of patients in many of whom electrocardiograms had been recorded shortly before death.

It was soon apparent that the relevant facts could not be obtained by reviewing old autopsy protocols or by employing the usual (Virchow) technique of pathologic examination. Consequently, a method of serial slicing and multiple microscopic sectioning was adopted. The more complete data thus made available proved difficult to describe and record accurately or to visualize clearly. It was necessary, therefore, to replace written protocols by pictorial records of the actual appearance of the serial slices. In addition, a method was devised for representing lesions schematically, aimed at illustration of the relevant pathologic facts and based on certain convenient characteristics of the ventricular anatomy, the epicardial ramifications of the coronary arterial tree, and the observed distribution of myocardial lesions. This permitted easy visual correlation of the data for any one heart as well as comparison of that heart with others of the series, and greatly expedited the organization of our material.

The results of clinicopathologic study of 200 cases by these methods form the subject matter of this study. Some of the findings have already been outlined in a preliminary communication.¹

Part I is concerned with the pathologic examination of the heart muscle: its importance, its difficulties, the errors which result from unawareness of the difficulties, and the methods of examination that are adequate to obtain the data necessary to answer the questions raised by modern clinical and electrocardiographic study.

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This investigation was aided by a grant from the Life Insurance Medical Research Fund, beginning July 1, 1947.

Part II deals with the problems of the recording and illustrating of the pathologic data for clinical and electrocardiographic correlation, and with the description of a schema which will be used to make the subsequent presentation of data easier and clearer.

In later sections of the report now in preparation, the electrocardiographic, pathologic, and clinical findings will be discussed.

THE IMPORTANCE OF THE MYOCARDIAL EXAMINATION

Precise localization of infarcts and scars in the heart muscle has not always been deemed important. The pathologists of the nineteenth century were more concerned with the nature than with the site of "fatty degeneration," "myomalacia cordis," "myocardial fibrosis," "ventricular aneurysm," and "coronary ossifications"—mysterious processes later unified under the concept of arterial sclerosis and occlusion with secondary myocardial infarction.² As long as "arteriosclerotic heart disease" was diagnosed only in the autopsy room, and coronary thrombosis was thought to be a rare and inevitably fatal event, it was not thought that muscle lesions required more precise description than analogous lesions in the spleen, kidney, or lung.

The combination, in 1918, of Herrick's description of coronary thrombosis as a clinical entity³ and Smith's experimental production of electrocardiographic changes by coronary ligation in dogs⁴ first stimulated general interest in localizing muscle lesions.* The key to the diagnosis of occlusive coronary artery disease during life was seen to lie in a proper interpretation of pain, and of certain electrical phenomena—both reflections, not of the silent arterial lesions themselves, but of their effect on the blood supply of cardiac tissues.

Since the limb-lead electrocardiogram, supplemented by a single precordial lead by Wolferth and Wood (1932),⁶ diagnosed dependably only certain massive lesions, no real need was seen for pathologic localization of damage beyond distinguishing "anterior," "posterior," and "lateral" damage of major proportions. For this the routine technique of autopsy seemed to suffice, and descriptions by Parkinson and Bedford (1929),⁷ Whitten (1930),⁸ and Barnes and Ball (1932)⁹ appeared to provide adequate anatomic generalizations.

As multiple precordial leads came into general use and more tracings were taken in cases suspected of coronary disease, it became clear that many electrocardiographic patterns could be distinguished besides those of classical "anterior," "posterior," and "lateral" infarction. Terms like "anteroseptal," "high lateral" and "posterolateral," "transmural," and "subendocardial" infarction entered cardiologic parlance.¹⁰ In addition, certain more sharply localized disturbances of the precordial ventricular complex were recognized frequently and attributed to myocardial damage.¹¹ It was assumed that these electrocardiographic patterns reflected areas of damage smaller than those resulting from high occlusion of a major vessel; that such damage conformed to well-known pathologic anatomic patterns; and that its presence or absence in any particular case was readily verifiable at necropsy by the average prosector.

*Herrick's original report (1912) excited surprisingly little interest, as he has observed.⁵

It has generally been forgotten that few detailed descriptions of the form and location of areas of myocardial damage exist in the standard texts or monographs on cardiac pathology, most of which were written before such information was of recognized importance. Despite the appearance of a host of clinicopathologic and electrocardiographic studies in the last two decades, the gap has yet to be filled. The reader who attempts to gain a clear conception of the type of lesion that is found at necropsy in patients suffering from angina pectoris or coronary thrombosis, or of the diagnostic efficiency of the multiple chest lead electrocardiogram, is overwhelmed by complex, confusing, or even contradictory data. When observers differ, there are no criteria for distinguishing good data from bad. When failures of correlation occur there is no way of telling whether they are due to defects of clinical study, of electrocardiographic analysis, or of the autopsy itself. The only hope of reconciling these inconsistencies is through balanced studies wherein equal skill and attention are directed to the clinical, electrocardiographic, and pathologic aspects of a large series of patients.

An essential first step is realization that the standard autopsy technique never was designed to answer the questions or check the diagnostic claims of present-day electrocardiographic and clinical study. However, without using any new pathologic techniques, much can be accomplished by redeployment of familiar methods. In particular, a systematic exploration of the ventricular muscle mass must be the central consideration of the autopsy whenever clinicopathologic and electrocardiographic correlation is intended; for the muscle lesions, in the present state of our knowledge, form the main bridge between clinical and pathological observations. The examination of the heart muscle is in itself exacting and treacherous, presenting certain problems which it will be well to consider before proceeding further.

PITFALLS OF THE MYOCARDIAL EXAMINATION

Adequate study of the heart at autopsy, especially if electrocardiographic correlation is intended, requires more time, patience, and attention to detail than are usually allocated. The gross anatomy of discrete lesions, their size, shape, and position, has to be determined accurately. Moreover, it is necessary for the prosector to bring a representative portion of every damaged area under the microscope for the ultimate determination of the nature and age of lesions. In practice, not only is it impossible to accomplish these things by a hasty or unsystematic dissection, but even a time-consuming study can result in wrong conclusions unless certain prevalent errors are specifically guarded against in every case. These errors are of three varieties:

1. *Lesions May Never Be Seen at All.*—Too often they are completely buried in the ventricular wall and only a slice through it will disclose them. The longitudinal cuts of the "Virchow" technique were never designed to expose large surfaces of muscle but were meant primarily to open the chambers and display the valves. Failure to make numerous regularly spaced cuts through the ventricular substance involves the risk of missing smaller or un-

usually placed lesions. These are more common than is generally realized. Moreover, early acute lesions may produce little or no gross change in the muscle. Consequently, the clinical history of pain, falls in blood pressure, or electrocardiographic changes must be available. The only indication for suspecting myocardial damage may be stenosis of a coronary branch.

2. *Lesions May Be Misinterpreted.*—Gross appearances are often deceptive. Recent infarcts may be confused with normal, autolyzed, incompletely fixed, or fatty muscle, or with vascularized scars. In the coronary arteries the significance of clots (ante-mortem or post-mortem), atherosclerotic plaques, or hemorrhages may not be clear. Error may be largely avoided if all gross diagnoses are checked by microscopic sections. Indeed, it is only through the microscopic study that we can establish with any certainty the age of myocardial or coronary lesions. Even so, very recent lesions, those less than six hours old, show no discernable histologic changes.¹² In these the functional state of the muscle can only be suspected from the implications of the coronary lesions and the clinical and electrocardiographic examinations.

3. *The Position and Anatomic Relationship of Lesions May Be Incorrectly Determined.*—In addition to finding damaged areas by dissection and identifying their nature by the microscope, it is necessary to establish their position and shape if correlation with the results of clinical diagnostic methods is intended. This is difficult or impossible when using the conventional methods of opening the heart. Once longitudinal cuts have been made in the ventricles, further slicing reduces them to bewildering fragments and the specimen becomes of little further use. It is then impossible for the prosector to relate accurately the lesions to the recognized cardiac landmarks. It is essential, therefore, to cut the heart thoroughly to pieces, yet provide for reconstruction of its original form by making the cuts in some standard way.

THE LITERATURE

Failure to avoid the pitfalls of the myocardial examination explains many of the confusing features of the recent clinicopathologic literature of coronary disease. Many seeming inconsistencies can be resolved by evaluating papers on the basis of the method of pathologic examination employed. Most studies fall into one of three groups: (1) those in which the authors have not personally examined their material but have used autopsy protocol data; (2) those in which the examination of the myocardium, though performed personally by the investigators, was subsidiary to an investigation of some other problem; and (3) those in which the examination was done personally by the investigators and a coordinated gross and microscopic study of the myocardium was the main objective. As one would expect, the data accumulated by these different methods are quite diverse.

1. The first type of study is notoriously unreliable. Routine dissections of the heart, even if not delegated to inexperienced apprentices, consist at best of a relatively thorough examination of the anterior left ventricular wall and apex, a cursory examination of the posterior wall, a few random cuts through

the ventricular muscle, and dissection of the first few centimeters of the main coronary arteries. Rarely are more than one or two microscopic sections of the muscle taken, and these may not be correlated with the gross findings. In other words, no effort is made to avoid the errors listed earlier.

It is fallacious to suppose that the mere size of any series will protect against errors. The mistakes of the routine autopsy protocol are not of the random variety that tend to cancel out; instead, the same types of error keep recurring. Easily found "anterior" infarcts or scars are reported as more common than "posterior" or "lateral" lesions which require more systematic search. The type of lesion found becomes stereotyped and oversimplified because those which do not conform to the prosector's idea of "anterior," "posterior," and "lateral" are crowded into one of these categories willy-nilly or else dismissed as "diffuse" or "patchy." One can, indeed, recognize studies based on routine autopsy protocols by the very character of the data they report.

Unfortunately, a large and increasing number of clinicopathologic studies fall into this first group, most often the work of investigators whose primary interest is electrocardiography. The sheer mass of the data has convinced many that the major pathologic problems of the muscle lesions in coronary disease are settled. The frequent inconsistency between clinical and pathologic observation is too often imputed to the lack of precision of clinical methods and not often enough to the pitfalls of the autopsy. The average clinician accepts the protocol at its face value and discounts his clinical findings accordingly. The average pathologist sees little reason for expending the time and work required for the revision of a pathologic method which has long been, and apparently still is, quite satisfactory to most clinicians.

2. The second type of investigation proceeds on the assumption that adequate myocardial data can be collected incidental to studies of other features of coronary disease. The major papers have been concerned primarily with coronary artery injection and perfusion for the determination of anastomoses and collateral circulation. The value of such studies for electrocardiographic and clinical correlation is very limited, though they have added much to knowledge of the coronary circulation. These methods have been employed by careful workers who have examined the hearts themselves and, consequently, who have found more lesions, both myocardial and coronary, than are reported in studies of the first type considered.

There have been unfortunate consequences of this work which have hindered rather than expedited adequate study of the heart muscle. The striking pictures provided by the radiopaque injection techniques have tended to diminish interest in the more prosaic myocardial exploration, giving rise to an impression that the hallmark of a thorough pathologic examination is a roentgenogram of an injected and "unrolled" specimen. Injection alone is no guarantee of a good necropsy. The errors mentioned before are just as likely to occur unless special precautions are taken. In addition there is great probability that the microscopic study will be distorted by the saline or thiocyanate perfusion that accompanies the injection.

Although the muscle examination performed after injection and unrolling of the heart cannot be entirely satisfactory, it can be done carefully enough to bring out the great variety of lesions that occur. In contrast to the oversimplified picture resulting from routine examinations, these investigators find an extremely complex situation. As a result, many workers feel that painstaking myocardial examination is scarcely worth the time because the vagaries of arterial anomaly, stenoses, occlusion, and collateral circulation lead to unpredictable variability in myocardial lesions. It seems probable that in a majority of cases the truth lies somewhere between the oversimplified and the hopelessly complex view.

3. The third group of papers is made up of studies by investigators who have personally examined hearts with the object of obtaining more information about the myocardium. The papers are not numerous and because of their importance are worthy of enumeration.

In their monograph, Büchner, Weber, and Haager (1935)¹³ present careful studies of the myocardium and coronary arteries in a series of forty-three cases. These findings were correlated only with standard limb-lead electrocardiograms. They distinguished sharply between patchy subendocardial and massive transmural lesions, attributing the former to "coronary insufficiency," but did not concern themselves greatly with localization beyond the conventional "anterior" and "posterior" sites.

About the same time Jervell (1935)¹⁴ reported a series of sixty-nine cases in which he carefully described and illustrated the lesions found in the coronary arteries and myocardium. The muscle lesions were only roughly localized, however, and he failed to note the relationship of lesions to the endocardial or epicardial surfaces of the heart. He used a single precordial electrode in addition to the standard limb leads.

Friedberg and Horn (1939)¹⁵ presented more evidence bearing on the problem of coronary insufficiency when they found thirty-seven cases of myocardial infarction without coronary thrombosis (among 119 acute infarcts) in a series of 2,000 autopsies. Each heart was carefully examined by the authors, special attention being given to the myocardial lesions. In these cases they emphasized the frequent occurrence of acute necrosis in the left ventricle, especially in the subendocardial regions or in areas of old scarring.

As a result of their interest in the muscle bundles of the ventricles, Robb and Robb,¹⁶ and Lowe¹⁷ have noted the tendency of myocardial lesions to run circumferentially in the wall of the left ventricle, often assuming the shape of a thin, curved plate. They claimed a special relationship between lesions and the muscle bundles and attempted electrocardiographic correlation on this basis.

In 1945 Pardee and Goldenberg¹⁸ re-examined the myocardium of twelve hearts rescued from the Pathology Department Museum of the New York Hospital. Besides attempting to determine the precise character and location of lesions, they paid special attention to the relationship of lesions to the endocardial and epicardial surfaces of the ventricles. These findings were correlated with electrocardiographic studies which included a single precordial lead.

In a few isolated case reports by Langendorf and Kovitz (1942),¹⁹ Price and Janes (1943),²⁰ and Pirani and Schlichter (1946)²¹ special study of the myocardium was carried out. The lesions they found were largely subendocardial in position. These they have reported as rarities, but further study has shown this to be a common finding.

The information accumulated by the investigators comprising the third group is different from that reported in most studies. Having diligently explored the myocardium, they have been impressed by a high frequency of discrete lesions, especially in the septal and posterolateral regions, as compared with the classical types; by the common occurrence of multiple lesions of different ages in the same heart; and by the practical limitation of damage to the left ventricle. Some have noted the frequency of subendocardial damage, often in the absence of coronary occlusion. All have found fewer discrepancies between clinical and electrocardiographic observations and the autopsy than are usually reported.

As a whole, these reports confirm the statement made earlier that careful study yields important information not obtainable by ordinary routine methods. They tend to invalidate the bulk of the literature without providing enough uniform data to fill its place. In addition, these reports are unsatisfactory for present-day electrocardiographic pathologic correlation studies because none have used multiple precordial leads and because their pathologic techniques, while superior to the routine autopsy, do not provide enough accuracy of localization. Hitherto this fact appears to have been recognized only by three groups of investigators.

In Kossmann and De La Chappelle's series of twelve cases (1938-1939),²² their pathologic method consisted of serially slicing the muscle and cross-sectioning the coronary arteries. Multiple microscopic sections were used to confirm the gross diagnosis. As far as we know, these are the first cases with multiple precordial lead electrocardiograms in which the pathologic examination was adequate.

Recently Myers, Klein, Stofer, and Hiratzka (1947)²³ have begun a series of reports based on a careful study of the myocardium. After studying 167 hearts at autopsy by the injection-dissection technique of Schlesinger,²⁴ they shifted to a serial slice, multiple microscopic section technique that leaves little to be desired. For correlation they have used multiple precordial lead electrocardiograms. As yet, the anatomic results of this study have not been published.

In 1939-1940 we became interested in this problem, and with the aid and encouragement of Dr. C. C. Wolferth and Dr. E. B. Krumbhaar, began a careful autopsy study of hearts in patients with coronary disease, especially those who had had thorough precordial lead electrocardiographic study. We adopted, as the best technique available, the serial slice method as used by Lowe and others (we were not then familiar with Kossmann and De La Chappelle's work). In this regard, it is interesting to note that Myers and associates have independently arrived at a pathologic technique similar to ours.

REQUISITES OF AN ADEQUATE TECHNIQUE

Because of the general lack of understanding of the importance and difficulty of the myocardial examination, it is urgent that definite criteria be established for estimating the adequacy of myocardial study. These will be useful not only as a guide to those performing the examination, but as a yardstick for those who read and evaluate papers based on anatomic studies. We have found the following general principles fundamental:

1. Large areas of muscle must be exposed in a systematic way.
2. The main epicardial branches of the coronary arteries must be carefully cross-sectioned at short intervals.
3. Carefully marked microscopic sections from the muscle and arteries must form the basis for the final decisions regarding age and localization of lesions.
4. The observer must keep himself oriented at all times so as to be able to correlate his various findings, gross and microscopic. To this end, the dissection should produce pieces suitable for reconstructing the heart easily.
5. Clinical and electrocardiographic data must be available at the time of the pathologic examination.
6. Nothing must be done that will impair the accuracy of microscopic study. In particular, saline perfusion or prolonged autolysis, both of which make interpretation of early acute infarction difficult, should be avoided.

SERIAL SLICE TECHNIQUE

It is difficult to satisfy these fundamental criteria without resort to a slicing technique. A method we can recommend after thorough study, the details of which will be given in later papers, can be outlined briefly as follows:

The heart is removed from the body intact. The coronary arteries are cross-sectioned at short intervals, and blocks for microscopic sections are cut from them. The ventricular myocardium is then cut into eight to twelve slices of uniform thickness in a plane perpendicular to the long axis of the left ventricle.* The blocks of tissue which are removed for the preparation of microscopic sections are carefully marked, and orientation is preserved by including the full thickness of the wall, endocardium to pericardium. The suspicion of muscle damage is eliminated or confirmed on the basis of microscopic study: the implications of the clinical, electrocardiographic, and coronary artery data are followed up in all cases but especially for the discernment of very recent damage, for the evaluation of ischemic states not necessarily causing histologic changes, and for the analysis of complex multiple lesions.

COMMENT

We began this study using a radiopaque injection technique for the study of the coronary arteries.²⁴ This method gives an excellent picture of the arterial

*So that the slices may be uniform, the heart is fixed in formalin or Klotz solution for twenty-four to forty-eight hours before slicing. A mechanical slicer is useful but not essential for this work. The auricles may be removed or not, as desired.

tree, best displayed by stereoscopic roentgenography of the uncut heart. Injection studies certainly add information about the completeness of severe narrowings and the presence or absence of larger anastomoses, under the conditions of post-mortem perfusion. However, they have certain disadvantages to which allusion has already been made. Saline or thiocyanate perfusion and delayed fixation, essential parts of the procedure, produce artefacts in the muscle which may seriously interfere with the histologic diagnosis of early acute infarction. The presence or absence of such early lesions is often a point on which the whole clinicopathologic interpretation of a case turns, yet they are admittedly the most difficult to evaluate. Additional knowledge of anastomoses does not seem sufficient justification for risking mistakes in this regard. In the final analysis the ability of collaterals to provide an adequate supply of blood can only be estimated by studying the condition of the muscle itself. The summation of the effects of fall in blood pressure, vasoconstriction, or changes in cardiac work and oxygen supply cannot otherwise be evaluated at necropsy in the present state of our knowledge. Because of these considerations we have abandoned injection of the coronary vessels except under special circumstances.

The problems of finding the location and character of myocardial lesions are of more than academic interest. The confused state of knowledge of the natural history of coronary disease stems directly from the failure to recognize and solve these problems. Though there are deficiencies in pathologic techniques which themselves call for research, it is not these primarily which are responsible for the confusion, but rather the failure to use known techniques well.

The principles we have outlined must be kept in mind when evaluating any clinicopathologic study of coronary disease. The reader would be wise to reject from serious consideration any studies based on routine autopsy protocols or those whose authors are not sufficiently cognizant of the pitfalls of the pathologic examination to make any mention of how or by whom it was done. He should eye with suspicion any article claiming to have obtained adequate facts about the myocardium if its study is incidental to some other type of investigation which might interfere with histology or complete dissection, for success under such conditions is most unlikely.

SUMMARY

Accurate localization of muscle damage at the autopsy is of fundamental importance for clinicopathologic correlation in coronary disease. Routine autopsy technique is unsuitable. Precise localization of muscle lesions requires not only thorough gross and microscopic scrutiny of the ventricular myocardium, but multiple cross-sectioning of the epicardial coronary arteries and reference to relevant clinical and electrocardiographic findings while dissecting the heart. Examinations less systematic than this fail to protect against serious errors which account for much inconsistency and confusion in the literature.

Although the number of clinicopathologic studies of coronary disease is large, adequate, detailed information about the state of the heart muscle is

seldom provided. Studies in which the myocardial examination has a central place, however, consistently report more lesions and show better correlation with clinical and electrocardiographic data. This investigation attempted to combine scrutiny of the ventricular myocardium with multiple precordial lead electrocardiograms and adequate clinical data in a series of 200 autopsied patients.

Attempts to modify existing pathologic methods have led to a technique, deserving of wider use, whereby the ventricular myocardium is explored by serial slices. Carefully located and oriented blocks of tissue removed from gross lesions and areas under suspicion are examined microscopically to determine the extent and nature of muscle changes and the state of the coronary vessels. While unsuited to routine use, this type of examination is a necessity for every case to be included in a clinicopathologic series aimed at electrocardiographic correlation. The present paper is concerned with the principles of an adequate pathologic examination in coronary disease and with description of the method used in our studies.

Since this paper went to press additional communications from Gordon Myers and his co-workers have been published in the *AMERICAN HEART JOURNAL* and will be considered in later sections of our report.

REFERENCES

1. Wolferth, C. C., Sayen, J. J., and Sheldon, W. F.: The Anatomy of Acute Infarcts and Scars in the Heart With Reference to Electrocardiographic Diagnosis, *Tr. A. Am. Physicians* 60:138, 1947.
2. Leyden, E.: Ueber die Sclerose der Coronar-Arterien und die davon abhängigen Krankheitszustände, *Ztschr. f. klin. Med.* 7:459, 539, 1884.
3. Herrick, J. B.: Concerning Thrombosis of the Coronary Arteries, *Tr. A. Am. Physicians* 33:408, 1918.
4. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22:8, 1918.
5. (a) Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59:2015, 1912.
(b) Herrick, J. B.: An Intimate Account of My Early Experience With Coronary Thrombosis, *AM. HEART J.* 27:1, 1944.
6. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183:30, 1932.
7. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14:195, 1928.
8. Whitten, M. B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, *Arch. Int. Med.* 45:383, 1930.
9. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* 183:215, 1932.
10. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
11. Wolferth, C. C.: The Clinical Significance of Precordial Leads in the Diagnosis of Heart Disease. Part II, *Mod. Concepts Cardiovas. Dis.* 15: (Feb.), 1946, American Heart Association, New York.
12. Mallory, G. K., White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction, *AM. HEART J.* 18:647, 1939.
13. Büchner, F., Weber, A., and Haager, B.: Koronarinfarct und Koronarinsuffizienz, Leipzig, 1935, Georg Thieme.
14. Jervell, A.: Elektrokardiographische Befunde bei Herzinfarct, *Acta med. Scandinav. Suppl. LXVIII*, 1935.
15. Freidberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J. A. M. A.* 112:1675, 1939.

16. Robb, J. S., and Robb, R. C.: Localization of Cardiac Infarcts in Man. I. A Comparison of Anterior-Posterior With Muscle Bundle Modes of Localization; II. Twenty-nine New Cases of Muscle Bundle Localization With Post-mortem Confirmation, *Am. J. M. Sc.* 197:7, 18, 1939.
17. Lowe, T. E.: The Significance of Myocardial Scars in the Human Heart, *J. Path & Bact.* 49:195, 1939.
Lowe, T. E.: Some Principles Governing the Supply of Blood to the Myocardium in Occlusive Arterial Disease, *AM. HEART J.* 21:326, 1941.
18. Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement, *AM. HEART J.* 30:367, 1945.
19. Langendorf, R., and Kovitz, B.: Acute Myocardial Infarction Without Deviation of the S-T Segment in the Electrocardiogram, *Am. J. M. Sc.* 201:239, 1942.
20. Price, R. K., and Janes, L. R.: A Case of Subendocardial Infarction, *Brit. Heart J.* 5:134, 1943.
21. Pirani, C. C., and Schlichter, J. G.: Subendocardial Myocardial Infarct, *Ann. Int. Med.* 25:847, 1946.
22. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction. I. Observations on Cases With Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, *AM. HEART J.* 15:70, 1938; II. Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, *AM. HEART J.* 18:344, 1939; III. Observations on Cases in Which the Lesions Were Diffuse, *AM. HEART J.* 18:352, 1939.
23. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, *AM. HEART J.* 34:785, 1947.
24. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15:528, 1938.

THE RELATION OF CARDIOVASCULAR DISEASE TO APOPLEXY

A REVIEW OF 155 CASES WITH AUTOPSY

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CEREBRAL vascular accident, or apoplexy, is now the third leading cause of death in this country, ranking only after heart disease and cancer. It has become increasingly evident that rupture of sclerotic arteries and thrombosis do not account for many of these accidents. Many infarcts are found in the absence of thrombosis, and Scheinker¹ has shown that many hemorrhages are the result of bleeding from the deep venous systems. These veins in the striatal and periventricular regions are vulnerable to disease,^{2,3} and show evidence of stasis and "vasoparalysis" in cases of hypertensive hemorrhage.⁴ The question arises whether these phenomena, which appear to be largely anoxic, are the result of systemic circulatory failure or of functional vascular changes in the brain.

The part played by spasm in cerebral vascular accidents and hypertensive encephalopathy has been shown clinically and experimentally to be perhaps the most important primary factor, by many workers, including De Takats,⁵ Russek and Zohman,⁶ Askey,⁷ and Echlin.⁸ The mechanism which stimulates the spasm is obscure. There are several possibilities. It may be an intrinsic neurovascular reaction of the hypertensive state. Emboli from the heart may possibly induce widespread spasm in other unoccluded branches of the cerebral arteries. The high blood pressure itself may cause a smooth muscle contraction in response to stretching.⁸ Circulatory anoxia may stimulate vasoconstriction, as suggested by the work of Trueta and associates,⁹ who demonstrated that prolonged arterial spasm often follows temporary ischemia in a tissue.

With these questions in mind, especially in relation to the possible role of systemic circulatory failure in the production of apoplexy, we undertook to analyze 155 cases of cerebral vascular accident confirmed by necropsy. Study was directed toward establishing the presence or absence of anatomic heart disease, congestive failure, other forms of circulatory failure, the hypertensive state, and cerebral vascular disease.

MATERIAL FOR STUDY

The material for this study consisted of 155 patients who died from apoplexy. They were studied at the Gallinger Municipal and Georgetown University Hospitals, Washington, D. C., and the United States Naval Medical Center, Bethesda, Md. In all instances the apoplexy was the cause of death or a major factor in bringing it about. The lesions were relatively acute and usually fairly large. The numerous cases of small, old infarcts, which are often seen at autopsy,

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were not included because the local vascular relationships could not be accurately analyzed. Our series contains no cases associated with rheumatic heart disease, only because none with fatal apoplexy were seen. Inflammatory diseases, including two cases of bacterial endocarditis with cerebral hemorrhage, were not incorporated in the study.

The brains were examined in the manner used in many pathological laboratories. The meninges, vessels, and superficial appearance were studied in the fresh state. After fixation in formalin the brain stem was removed by section through the midbrain. The forebrain was cut serially in frontal sections about 0.5 to 1.0 cm. in thickness. The brain stem and cerebellum were similarly cut, but the sections were thinner. Appropriate microscopic examinations were made from the lesions as well as from apparently normal regions. Paraffin-embedded material stained with hematoxylin and eosin was most often employed, but phosphotungstic acid hematoxylin, myelin sheath, and Bodian stains were sometimes used.

For purposes of analysis the patients fell into four arbitrary categories: those with hemorrhage, infarction with thrombosis, infarction without thrombosis, and ruptured aneurysm (see Table I).

TABLE I. CEREBRAL LESIONS IN 155 CASES OF APOPLEXY

Hemorrhage	118
Infarction with thrombosis	12
Infarction without thrombosis	11
Ruptured aneurysm	14

The cases are summarized in Table II, where clinical and pathologic data pertinent to the study are recorded. In this table, under "hypertension," the highest blood pressure found on admission to the hospital is noted, and its duration recorded when it was known. So far as could be determined, the high blood pressure preceded rather than resulted from the apoplexy in all cases where it was present.

Tables III and IV record the statistical data relative to the coexistence of cardiovascular disease and apoplexy. In addition, certain other facts of clinical interest are tabulated.

The hypertensive state was present in most of the patients with hemorrhage and infarction. It was also present in eight of fourteen patients with aneurysm. A definite history of congestive heart failure could be elicited in surprisingly few of the patients with hemorrhage, despite the fact that the majority had cardiac hypertrophy and coronary sclerosis. Eleven of the twenty-three patients with infarction, however, had heart failure, and two more died directly as a result of a precipitous drop in blood pressure which infarcted the brain.

Cerebral thrombosis was reported in only one patient with hemorrhage (Case 47A569) and in twelve of twenty-three instances of infarction. Mural thrombi in the heart were reported in none of the patients with hemorrhage, and in only three of the patients with infarction (Cases N30858, N29857, and N47-275). Almost all the hemorrhages were deep in the cerebral hemispheres,

TABLE II. CLINICAL AND PATHOLOGIC FINDINGS IN 118 CASES OF APOPLEXY

NO.	AGE	SEX	DE-SCENT	DURATION OF STROKE	HYPERTENSION AND DURATION	HEART DISEASE	LOCATION
<i>Cerebral Hemorrhage</i>							
47A569	72	M	N	7 days	176/112	400*	l. cerebral, i. v.
47A31	47	M	N	days	1 yr., 230/120	hyp.*	bil. perivent., i. v.
47A569	72	M	N	6 days	6 yr., 176/112	400*	r. cerebral, i. v.
47433	57	F	N	3 days	3 yr., 240/145	300	subarachnoid
50Y47	69	M	J†	4 days	?	hyp.	r. cerebral, i. v.
62Y47	63	M	W	2 days	10 yr., 220/120	hyp.*	l. cerebral
47251	47	M	N	hours	3 yr., 250/120	260*	l. cerebral, i. v.
47A95	47	M	N	5 hr.	170/128	800*	l. cbllm., i. v.
47A183	49	M	N	2 days	5 yr., 240/140	575*	l. cerebral, i. v.
A47-2	45	F	N	2 hr.	300/90	490	cbllm., pons
47-27	57	M	N	1 day	5 yr., 240/180	350*	r. cerebral, i. v.
A47-9	50	F	N	1 day	1 yr., 290/160	475*	l. cerebral, i. v.
46A73	35	F	N	2 hr.	none	normal	subarachnoid
46A89	46	F	N	2 hr.	260/120	380*	l. cerebral, i. v.
46A106	54	F	N	2 hr.	6 yr., 260/130	550	l. cerebral, i. v.
46A114	42	M	N	2 hr.	2 yr., 280/160	600*, c. f.	l. cerebral, i. v.
46A124	60	M	N	2 hr.	290/150	410*	i. v.
46A142	59	F	N	8 days	250/150	640*	l. cerebral, i. v.
46A284	72	M	N	1 day	185/85	275*	l. cerebral, i. v.
46A300	54	M	N	hours	260/145	650*	l. cerebral, i. v.
46A321	48	M	W	hours	280/200	510*	r. cerebral, i. v.
46A362	68	M	N	hours	?	425*	l. cerebral, i. v.
46A370	72	M	N	hours	240/140	550*, c. f.	l. cbllm., i. v.
46A374	38	F	N	2 days	3 yr.	380*	r. cerebral, i. v.
45A36	57	F	N	12 hr.	3 yr., 120/0	650*, c. f.	l. cerebral, i. v.
45A47	55	F	N	4 days	5 yr.	370*	pons
45A57	50	M	N	3 days	180/120	350*	l. cerebral
45A279	48	M	N	4 days	140/100	400*	l. cerebral
45A281	55	F	N	24 hr.	1 yr., 240/150	375*	r. cerebral, i. v.
45A341	53	M	N	24 hr.	5 yr., 230/160	650*	l. cerebral
45A380	65	M	N	hours	4 yr., 220/?	650*	cerebral, i. v.
44A54	57	F	W	4 days	1 yr., 235/95	300*	r. cerebral, i. v.
44A64	33	F	N	24 hr.	4 yr., 260/140	360*	i. v.
44A111	745	F	N	4 hr.	240/140	575	l. cerebral, i. v.
44A160	47	F	N	24 hr.	1 yr., 200/110	400*, c. f.	i. v.
44A206	58	F	N	4 days	160/100	350*	subarachnoid
44A212	40	F	N	hours	260/140	470*	i. v.
44A270	50	M	N	2 days	3 yr., 250/150	550*	l. cbllm., i. v.
44A293	74	M	W	hours	1 yr., 210/110	375*	l. cerebral, i. v.
44A312	43	M	N	7 hr.	3 yr., 200/140	700*, c. f.	pons, i. v.
44A342	50	F	N	2 hr.	262/150	375*	r. cerebral
44A344	49	F	N	4 days	1 yr., 240/150	425*, c. f.	l. cerebral
44A350	70	F	N	hours	1 yr.	340*	l. cerebral
44A351	58	M	N	12 hr.	244/170	630*	l. cerebral, i. v.
44A413	58	M	N	9 days	1 yr., 160/105	300*, c. f.	l. cerebral, i. v.
43A101	69	M	N	5 days	1 yr., 200/100	440*	subarachnoid
43A139	62	F	W	7 days	230/118	470*	r. cerebral
43A306	40	F	N	4 days	230/150	430*	l. cerebral
43A341	50	F	N	5 hr.	4 yr., 286/136	525*	l. cerebral
42A25	45	F	N	3 hr.	1 yr., 260/140	715*, c. f.	r. cerebral, i. v.
42A136	64	M	N	2 days	1 yr., 190/100	500*	r. cerebral, i. v.
42A139	41	F	N	7 hr.	1 yr., 208/120	625	r. cerebral, i. v.
42A146	43	M	N	2 hr.	1 yr., 200/100	550	l. cerebral, i. v.
42A281	45	F	N	8 hr.	240/110	400	l. cerebral
42A328	43	M	N	hours	240/150	430*	subarachnoid
42A379	64	F	N	3 days	260/110	350*	r. cerebral
42A405	63	M	N	8 days	220/150	550	r. cerebral, i. v.
41A81	49	M	N	5 days	125/40	400	i. v.
41A104	75	F	W	hours	1 yr., 260/120	425*	i. v.

†For abbreviations throughout Table, see footnotes at end of Table II.

TABLE II. CLINICAL AND PATHOLOGIC FINDINGS IN 118 CASES OF APOPLEXY—CONT'D.

NO.	AGE	SEX	DE-SCENT	DURATION OF STROKE	HYPERTENSION AND DURATION	HEART DISEASE	LOCATION
41A173	48	F	N	1 day	1 yr.	575	cerebral, i. v.
41A252	70	M	W	7 hr.	270/130	595*	l. cerebral, i. v.
41A300	47	M	N	24 hr.	220/100	475	i. v.
40A36	25	F	N	4 wk.	220/120	?	r. cerebral, i. v.
40A162	39	F	N	9 hr.	300/140	450	l. cerebral, i. v.
40A213	48	M	W	hours	235/140	575	r. cerebral, i. v.
40A242	38	F	N	?	240/110	410	r. cerebral, i. v.
39A26	39	F	W	?	242/158	hyp.	r. cerebral
39A111	50	F	N	7 hr.	250/130	hyp.	cerebral, i. v.
39A165	63	F	N	hours	186/84	300	r. cerebral, i. v.
39A167	62	F	N	2 days	300/160	hyp.	r. cerebral, i. v.
39A178	42	F	N	hours	1 yr., 220/120	500*	r. cerebral, i. v.
38A188	70	M	N	3 days	155/85	475	bilat. cerebral
38A265	70	F	N	2 days	5 yr., 260/140	475*	r. cerebral, i. v.
38A330	60	F	N	12 hr.	230/125	325	r. cerebral, i. v.
37A46	34	M	N	hours	250/120	615*	i. v.
37A124	30	M	N	15 hr.	210/112	350*	i. v.
37A128	59	M	N	1 day	200/150	675*	r. cerebral
3Y42	44	F	N	8 hr.	3 yr., 250/120	hyp.	subarachnoid
15Y42	50	M	W	hours	210/130	hyp.	l. cerebral, i. v.
47Y42	81	M	W	4 days	220/110	hyp.*	l. cerebral, i. v.
10Y43	49	F	W	7 days	210/95	hyp.	subarachnoid
7Y44	31	F	W	2 days	none	normal	multiple
99Y41	33	F	W	8 hr.	220/140	hyp.*	i. v.
34Y41	54	M	W	9 hr.	230/130	hyp.*	r. cerebral, i. v.
18Y41	55	M	W	2 days	250/140	hyp.*	r. cerebral
14Y41	77	F	W	3 days	years, 260/140	hyp.*	r. cerebral
20Y40	58	F	N	19 days	210/130	normal	r. cerebral, i. v.
18Y39	19	M	W	2 days	?	hyp.	r. cerebral, i. v.
78Y38	57	M	W	15 days	5 yr., 210/136	hyp.*	r. cerebral, i. v.
57Y38	37	M	W	hours	2 yr., 240/135	hyp.*	l. cerebral, i. v.
59Y37	53	F	N	hours	194/128	hyp.	r. cerebral, i. v.
57Y37	54	M	N	3 hr.	230/110	hyp.	l. cerebral, i. v.
55Y35	31	M	W	9 days	4 yr., 195/120	350	subarachnoid
36102	41	F	N	hours	?	720*	subarachnoid
36203	56	M	N	1 day	205/140	375	i. v.
36265	26	M	N	hours	170/70	350	r. cerebral, i. v.
35-421	45	F	N	12 hr.	235/140	475	l. cerebral, i. v.
44Y34	40	F	W	2 days	190/100	450	r. cerebral
N29070	50	M	W	6 wk.	4 yr., 150/?	510*	bil. cerebral, pons
N28681	53	M	W	5 days	3 yr.	420*	r. cerebral, i. v.
N28415	44	M	W	?	?	630*	r. cerebral, i. v.
N28411	745	M	W	?	180/120	410	r. cerebral, i. v., pons
N30743	76	M	W	1 day	?	425*	r. cerebral, i. v.
N30638	51	M	W	hours	260/170	470*	l. cerebral, i. v.
N29987	50	M	W	?	4 yr., 230/140	650*	r. cerebral
N29827	55	M	W	1 day	1 yr., 285/145	475*	l. cerebral, pons, i. v.
N47507	76	M	W	1 wk.	years, 170/86	510*	l. cerebral
N471186	73	M	W	3 days	270/150	475*, c. f.	cbllm., pons
N471111	77	M	W	2 wk.	hypertension	520*, c. f.	r. cerebral
N47302	56	M	W	3 days	180/120	375*, c. f.	l. cerebral
N47300	59	M	W	4 days	4 yr., 270/160	860*, c. f.	r. cerebral
N472798	76	M	W	2 days	10 yr., 180/80	450*	r. cerebral, brain stem
N472467	22	M	N	2 hr.	none	360	l. cerebral, i. v.
N472257	52	M	W	1 day	6 yr., 260/164	540*	r. cerebral
N472161	55	M	W	1 day	240/160	590*, c. f.	l. cerebral
N473959	56	M	W	2 days	158/92	410*, c. f.	l. cerebral, i. v.
N473697	65	M	W	9 days	176/116	430*	r. cerebral, i. v.
N4867	58	M	W	1 day	250/125	510*	r. cerebral

TABLE II. CLINICAL AND PATHOLOGIC FINDINGS IN 118 CASES OF APOPLEXY—CONT'D.

NO.	AGE	SEX	DE-SCENT	DURATION OF STROKE	HYPERTENSION AND DURATION	HEART DISEASE	LOCATION
<i>Infarction Without Thrombosis</i>							
47A327	51	M	W	days	? years	normal	r. parietal
A4731	44	F	N	8 days	none	350, c. f.	l. cerebral
47A559	62	M	W	6 days	20 yr.	600*	l. striatal
47A553	82	F	W	2 wk.	10 yr., 200/90	450*	r. front., pons
A47302	74	M	N	48 hr.	190/110	380*	l. cerebral
472102	54	M	W	2 days	2 yr., 180/115	640*, c. f.	r. cerebral
472870	55	M	W	7 days	1 yr., 160/100	395*, c. f.	r. parietal
NA1464	60	M	W	2 days	2 yr., 200/120	530*	multiple
NA4877	43	M	I	1 day	3 yr., 240/135	410*	diffusé
N30858	48	M	W	5 wk.	years, 125/100	460*, c. f.	r. cerebral
N4895	68	M	W	3 days	years	440*, c. f.	multiple

Infarction With Thrombosis

N28277	64	M	W	4 days	years	615*	r. mid. cerebral
N30750	69	M	W	25 days	160/90	304	l. mid. cerebral
N30527	22	M	W	29 days	142/100	540	vein of Galen
N30414	49	M	W	4 days	15 yr., 195/90	830*, c. f.	bil. mid. cerebral
N29857	?	M	W	10 days	170/120	640*, c. f.	multiple, cerebral
N47275	47	M	W	2 days	14 yr., 170/100	450*, c. f.	r. mid. cerebral
N47125	82	F	W	2 days	none	365*	l. mid. cerebral, superior cblm.
N4834	74	M	W	1 day	170/110	390*	l. mid. cerebral
N4828	67	M	W	6 days	years, 200/100	390*	r. mid. cerebral
N472254	54	M	W	3 days	224/108	410*	r. cerebral veins
A4065	81	M	W	days	160/120	500*, c. f.	r. mid. cerebral
47A7	77	F	W	2 days	150/100	470*, c. f.	r. mid. cerebral

Ruptured Aneurysm

NO.	AGE	SEX	DE-SCENT	HYPERTENSION AND DURATION	HEART DISEASE	LOCATION
N472789	52	M	W	150/98	385*	1.0 cm. from origin l. ant. cerebral
N472205	27	M	W	4 yr., 185/130	500	(1) 5.0 cm. from origin l. ant. cerebral, (2) 5.0 cm. from origin mid. cerebral (unruptured)
N471133	27	M	N		385	5.0 cm. from origin l. mid. cerebral
N47801	25	M	N	135/75	445	l. int. carotid just proximal to mid. cerebral
N30527	22	M	W	142/100	540	bifurcation of basilar
N28111	24	M	W	138/80	335	junction l. ant. cerebral and ant. communicans
N26170	53	M	W	200/120	500	junction of r. ant. cerebral and carotid
N22148	39	M	W	120/60	420	l. post. cerebral proximal
N21550	29	M	W	136/78	320	r. ant. cerebral just distal to communicans

TABLE II. CLINICAL AND PATHOLOGIC FINDINGS IN 118 CASES OF APOPLEXY—CONT'D.

NO.	AGE	SEX	DE- SCENT	HYPERTENSION AND DURATION	HEART DISEASE	LOCATION
<i>Ruptured Aneurysm</i>						
N21027	27	M	W	3 yr., 160/90	430	r. ant. cerebral just distal to ant. communicans
N21431	55	M	W	2 yr., 170/106	450*	junction r. mid. cerebral and carotid
48A111	51	F	N	190/120	560	l. internal carotid, intracranial
14Y35	56	F	N	115/85	250	r. mid. cerebral
48A129	52	F	W	years	350*, hyp.	ant. communicans

*Coronary arteriosclerosis.

Numbers under "Heart Disease" indicate the heart weight in grams.

c.f., congestive failure.

hyp., cardiac hypertrophy.

bil. perivent., bilateral periventricular.

cblm., cerebellum.

i.v., intraventricular.

h., hemisphere.

W, white.

N, Negro.

J, Japanese.

I, Native of India.

TABLE III. CARDIOVASCULAR FINDINGS IN CEREBRAL HEMORRHAGE

	NUMBER OF CASES	PER CENT
<i>Exclusive of Ruptured Aneurysm (118 Cases)</i>		
Hypertension*	105	89
Coronary sclerosis and/or cardiac hypertrophy†	97	82
Congestive heart failure	15	13
Dead within twenty-four hours of onset	64	54
Intraventricular hemorrhage	77	65
Intraventricular hemorrhage and dead within twenty-four hours of onset	51	66% of 77
Cerebral arteriosclerosis, marked	20	17
<i>Resulting From Ruptured Aneurysm (14 Cases)</i>		
Hypertension*	8	
Coronary sclerosis and/or cardiac hypertrophy†	7	
Cerebral arteriosclerosis, marked	3	

*History of hypertension, or diastolic pressure in excess of 90 mm. of mercury.

†Hypertrophy described by the pathologist, or the heart weighed 500 grams or more.

TABLE IV. CARDIOVASCULAR FINDINGS IN TWENTY-THREE CASES OF INFARCTION OF BRAIN

Thrombosis (total)	12
Arterial	10
Venous	2
Hypertension	11
Hypertension and heart failure	5
No hypertension or heart failure	1
No thrombosis (total)	11
Hypertension	10
Hypertension and heart failure	5
Heart failure without hypertension	1
Infarction following sudden systemic circulatory failure	2

65 per cent of them intraventricular, that is, in the distribution of the deep venous systems. While two-thirds of these patients with ventricular hemorrhage were dead within twenty-four hours, the other third survived longer, sometimes for more than a week. Obviously in these patients the intraventricular part of the hemorrhage was the culmination of a more slowly developing process. A well-developed cerebral arteriosclerosis was reported in only twenty of the 118 subjects with hemorrhage, and was scant or, rarely, absent in the remainder. It was altogether absent in eight of fourteen patients with ruptured aneurysm. No data were available concerning capillary fragility or prothrombin times in any of the patients. None of them received rutin.

Of additional interest in the patients with hemorrhage were the findings of marked obesity in only 28 per cent, while 80 per cent had nephrosclerosis of varying degrees.

DISCUSSION

It appears from this study that intrinsic functional vascular disease of the brain is the major factor in the pathogenesis of infarction and hemorrhage. Systemic circulatory failure could not be shown to be a direct cause in the majority of patients. In the cases of hemorrhage the lesions were usually deep in the cerebral hemispheres in and around the ventricles, the type emphasized by Scheinker,¹ and therefore not the result of "hypertensive rupture of an artery." This finding is further supported by the low incidence of marked arteriosclerosis in these patients. The possible aggravating effects of capillary fragility¹⁰ and altered clotting mechanisms upon the bleeding are not known.

The mechanism by which these hemorrhages are brought about seems, at present, to be arterial spasm, which produces anoxic damage to the vulnerable deep vessels, diapedesis, and coalescence of the hemorrhages.

Aneurysms resulting in apoplectic hemorrhage were included in the study because they often appear to be part of the hypertensive complex. They differ considerably from other forms of cerebral accidents in that spasm, circulatory failure, and vascular occlusion play no part in their genesis. Rather, they seem to be the consequence of the mechanical effects of high blood pressure in many instances, as some 50 per cent of the patients exhibited hypertension. Forbus,¹¹ in a study of aneurysms, pointed out that they "are acquired lesions arising from a combination of focal weakness in the vessel wall resulting from a congenital muscularis defect, and a degeneration of the internal elastic membrane due to continued overstretching of this membrane." His patients also showed a high incidence of hypertension and cardiac hypertrophy.

In the patients who had infarction with thrombosis, the mechanism is clear. Where the infarctions were found in the absence of thrombosis, only two explanations are at present possible: local vascular spasm or systemic circulatory failure. In two instances the systemic failure was the direct cause of the extensive infarctions, but in almost all other instances the only explanation was primary spasm in the cerebral vascular tree.

Four cases from the series are cited in some detail here to illustrate circulatory failure and local spasm in the production of infarction. Two are cases of

extensive infarction which followed a precipitous fall in blood pressure which came about after certain therapeutic measures. The other two are best explained on a basis of vascular spasm in the brain.

CASE 1 (No. N47-1464).—A 60-year-old white man came to the hospital complaining of cramps in his legs of two weeks' duration. He had had hypertensive heart disease with exertional dyspnea for two years. The leg cramps were treated with bilateral paravertebral sympathetic blocks, which brought down his blood pressure from 200/120 to 130/84. He became comatose, convulsive movements and hyperthermia followed, and death resulted in about forty-eight hours. At autopsy there were multiple acute hemorrhagic infarcts of the left cerebellar hemisphere, brain stem, right striatal region, and frontal lobes. Slight arteriosclerosis of the intracranial arteries was present, but there was no occlusion by this process or by thrombi. There was marked obstruction of both popliteal arteries by arteriosclerosis, but gangrene was not present.

The development of multiple hemorrhagic infarcts throughout the brain following a sudden fall in blood pressure illustrates the genesis of infarction by a rapidly failing systemic circulation.

CASE 2 (No. NA48-77).—A 43-year-old Indian had had hypertension for three years, and blurred vision, headache, and agitation for ten days before hospital admission. In the hospital he was given 0.3 Gm. of sodium amytal intramuscularly. His blood pressure fell from 240/135 to 190/110. Two days later his blood pressure was 235/155, and the therapy was repeated, with a drop in pressure to 100/70. Coramine was administered and the pressure rose to 210/130 but fell spontaneously the next day to 95/0. Oliguria developed and 1,000 c.c. of plasma was given. The blood pressure rose to 130/85, but the patient expired less than twenty-four hours after the fall in blood pressure to 95/0.

At autopsy there was scant cerebral arteriosclerosis. There was diffuse evidence of early ischemic necrosis, especially in the left temporal and parietal lobes. Acute destruction of cortical neurons and early disintegration of white matter, with numerous small perivascular hemorrhages, were seen. The heart showed coronary sclerosis but no acute disease.

The case again illustrates the effect of rapid circulatory collapse in a hypertensive patient. Severe destructive lesions in the cerebrum developed. The heart and kidneys (oliguria) may also have been functionally damaged in the process, but significant morphologic changes did not develop.

CASE 3 (No. N47-2102).—A 54-year-old Negro man became suddenly stuporous, then comatose, and died in less than forty-eight hours. He had had hypertensive and coronary heart disease, with mild failure, for two years. On admission his blood pressure was 180/115 and a gallop cardiac rhythm was present. Acidosis, uremia, hyperglycemia, and hyperpyrexia developed a few hours before death: conditions which had not existed previously. At autopsy there was early infarction of the whole right cerebral hemisphere, including the frontal, temporal, and occipital lobes, the striate region, the thalamus, and the hypothalamus. Considerable arteriosclerosis of the arteries of the brain, especially of the right internal carotid, was present, but there was no occlusion.

The case demonstrates massive infarction, in the absence of occlusion, of an entire half of the forebrain, in the distribution not only of the anterior, middle, and posterior cerebral arteries but also of other branches supplying the thalamus and hypothalamus. The patient was hypertensive and in failure. Two explanations are possible. One is that systemic circulatory failure, superimposed upon a cerebral blood supply already embarrassed by sclerosis, especially on the right, may have caused the lesion. The other is the presence of widespread spasm limited to half of the forebrain. Possibly both mechanisms were responsible.

CASE 4 (No. N30-858).—A 48-year-old white man had hypertensive heart disease of unknown duration. About a month before he died he developed a hemiplegia, which was followed by an episode of acute congestive heart failure. Sixteen hours before death an embolic thrombosis of his superior mesenteric artery occurred, and he died in shock. This embolus was confirmed at autopsy, and a large, friable thrombus was found in his left atrial appendage. The brain revealed extensive infarction, about one month old, in the distribution of the right middle cerebral and

anterior choroidal arteries. There was only moderate arteriosclerosis of the larger arteries at the base of the brain and almost none in the smaller vessels. No gross occlusion or thrombosis was present.

This case illustrates probable spasm in the distribution of two major arteries of the brain in a patient with hypertensive heart disease. The auricular thrombus and mesenteric embolism strongly suggest that a tiny embolus to the brain, which could not be demonstrated, may have initiated the probable spasm. Severe systemic circulatory failure does not seem to have been a factor, because there was no evidence that an episode of this sort preceded the stroke.

The presence of anatomic heart disease, sometimes severe, in many of these patients poses a problem which is still unsolved. That problem is, do transient episodes of circulatory failure, clinically unrecognized during the course of hypertension, precipitate cerebral anoxic vasospasm leading to apoplexy? Case 1 suggests that possibility, because the infarcts were focal and developed in the presence of general circulatory failure.

SUMMARY

One hundred fifty-five patients who died from apoplexy were studied in relation to associated cardiovascular disease. Hypertension was present in nearly 90 per cent. Functional cerebrovascular disease (probably spasm) appeared to be the important factor in most cases, while systemic circulatory failure accounted directly for very few cerebral accidents. A cause and effect relationship was entertained in patients with cerebral aneurysm with hypertension.

REFERENCES

1. Scheinker, I. M.: Alterations of the Cerebral Veins in Hypertensive Brain Disease and Their Relation to Cerebral Hemorrhage, *Arch. Neurol. Psychiat.* 54:395, 1945.
2. Finely, K.: Perivenous Changes in Acute Encephalitis Associated With Vaccination, Variola, and Measles, *Arch. Neurol. & Psychiat.* 37:505, 1937.
3. Schlesinger, B.: The Venous Drainage of the Brain With Special Reference to the Galenic System, *Brain* 62:274, 1939.
4. Aring, C. D.: Vascular Diseases of the Nervous System, *Brain* 68:28, 1945.
5. De Takats, G.: Emergency Treatment of Apoplexy, *J. A. M. A.* 136:659, 1948.
6. Russek, H. I., and Zohman, B. L.: Cerebral Angiospasm, *J. A. M. A.* 136:930, 1948.
7. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, *AM. HEART J.* 31:131, 1946.
8. Echlin, F. A.: Vasospasm and Focal Cerebral Ischemia, *Arch. Neurol. & Psychiat.* 47:77, 1942.
9. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L.: Studies of the Renal Circulation, Springfield, Ill., 1947, Charles C Thomas, Publisher.
10. Griffith, J. Q., and Lindauer, M. A.: Increased Capillary Fragility in Hypertension: Incidence, Complications, and Treatment, *AM. HEART J.* 28:758, 1944.
11. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, *Bull. Johns Hopkins Hosp.* 47:239, 1930.

OBSERVATIONS ON THE SPATIAL VECTORCARDIOGRAM IN MAN

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THE work reported herein was undertaken in order to investigate by means of the spatial vectorcardiogram the changes in electromotive force accompanying the heart cycle in man.

The vectorcardiogram is a record of the resultant manifest potential of the heart as it changes throughout the cardiac cycle, considered as a vector function of time. From the QRS complexes of the three standard limb leads, Einthoven, Fahr, and De Waart,¹ in 1913, determined vectors at ten equally spaced instants in the QRS interval. This method was modified in 1920 by Mann,² who, by joining the heads of these vectors with a continuous line, obtained records which were later termed vectorcardiograms. Use of the cathode-ray oscillograph for recording the vectorcardiogram in the frontal plane was first described in this country by Wilson, Johnston, and Barker, in 1937.³ Unknown to them, its use for this purpose had been described the previous year in Germany by Schellong.⁴ Adapting this method to three dimensions, Sulzer and Duchosal^{5,6} and Rochet and Vastesaeager^{7,8,9} constructed wire models of the spatial vectorcardiograms. Wilson suggested the equilateral (regular) tetrahedron as a convenient reference system for the mean QRS, T, and gradient vectors in space, and in 1947 reported an earlier study in which this reference system was applied to a human cadaver.¹⁰

Because of the complex nature of the generation of electric potentials in the heart and of the processes of conduction throughout the body, some objections may be raised to almost any spatial system which is proposed. It is obvious that the body cannot accurately be represented by any regular geometric figure. However, experience has shown that the Einthoven triangle is satisfactory for electrocardiography in the frontal plane. If a fourth electrode, placed somewhere on the back, could be considered as remote electrically from the source of potential as the three limb electrodes, these four electrodes would define the apices of a tetrahedron. The equilateral tetrahedron was adopted for the present study because it is a spatial reference system requiring the fewest electrode positions and because it permits the use of the Einthoven triangle as the frontal face

Aided by the Life Insurance Medical Research Fund, the Mrs. E. J. Caire Fund for Cardiovascular Research, the Helis Institute for Medical Research, and War Department Contract No. W-49-007-MD-389.

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and the application of the Einthoven concept to each of the other faces. Although the magnitude of the error inherent in this method has not been determined as yet, it is probably not too large for physiological purposes.

METHOD

The standard limb electrodes and a back electrode placed approximately three centimeters to the left of the spinous process of the seventh dorsal vertebra were used. Records of the spatial vectorcardiogram projected onto the frontal plane were obtained photographically during a single heart cycle by the method described by Wilson.¹¹ The arrangement of the apparatus for recording in the frontal and sagittal planes is shown in Fig. 1. The electrical impulse from the

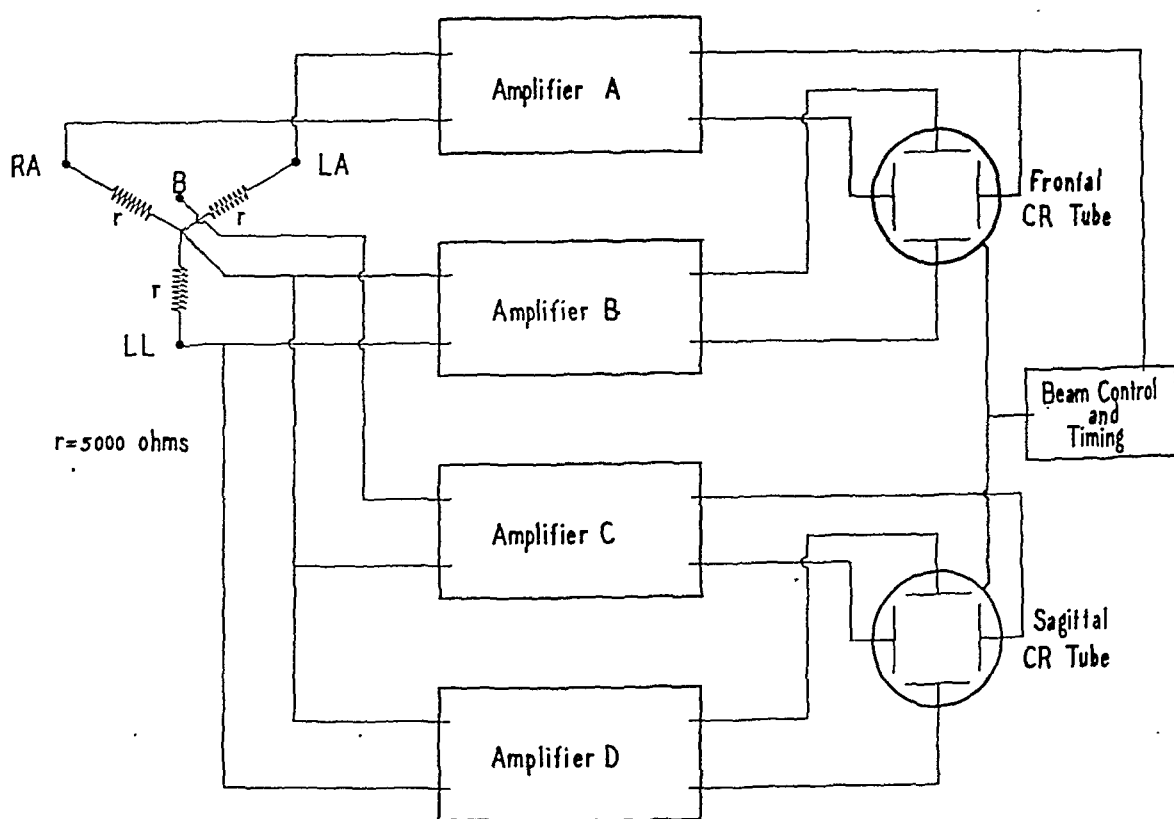


Fig. 1.—Schematic diagram of apparatus.

standard Lead I was amplified by Amplifier A of the similar four-stage push-pull resistance-capacitance coupled amplifiers to produce horizontal deflection of the electron beam of the cathode ray tube. The electrical impulse from the central terminal to the left foot was amplified by Amplifier B to produce vertical deflection of the electron beam. The connections were arranged so that deflection to the left of the frontal plane resulted when the left arm was positive with respect to the right arm, and a downward deflection resulted when the foot was positive with respect to the common terminal of the three 5,000-ohm resistors. The amplifiers were calibrated so that one millivolt across the input terminals of Amplifier A produced one inch deflection of the fluorescent spot on the oscillo-

graph screen, and one millivolt across the input terminals of Amplifier *B* produced 1.7 inches deflection. The beam control and timing circuit could be adjusted to turn on the electron beam for any desired interval during the heart cycle, and to modulate its intensity for timing and for indicating the direction in which the vectorcardiogram was traced.

By selection of the proper electrode combinations the projections onto the other surfaces of the tetrahedron were obtained similarly.

The projection onto a sagittal plane which intersects the frontal plane along its vertical axis was obtained on the second cathode ray tube simultaneously with the recording on the frontal plane. The horizontal deflection was produced by the electrical impulse between the central terminal of the frontal plane and the back electrode, the calibration being 1.2* inches per millivolt, and the vertical deflection was produced by the impulse between the central terminal and the foot electrode, that calibration being 1.7* inches per millivolt.

Construction of Models.—In order to facilitate visualization of the spatial relationship of the P, QRS, and T components of the vectorcardiograms, wire models were constructed. These were made by manipulating lengths of wire into shapes whose shadows, projected onto the various planes of an equilateral tetrahedron, conformed to the records actually obtained in the respective planes. In most of the normal subjects, models could be accurately constructed from records in the frontal and sagittal planes only, but comparisons with records obtained in the superior, left, and right planes were made for confirmation.

RESULTS

Normal Subjects.—The subjects were sixteen normal male medical students.¹² Although the records showed considerable variation from subject to subject, most of them had certain characteristics in common. A hypothetical normal vectorcardiogram with average values and representative characteristics is described (Fig. 2). It consists of three $s\hat{E}$ -loops, representing the terminus of the changing vector in the P, QRS, and T complexes, respectively.†

It will be apparent that the $s\hat{E}$ -loops are not necessarily closed figures, as each loop may terminate some distance from its point of origin in space. Thus, there is not necessarily a fixed origin for the instantaneous vectors.

For indicating their orientation, these loops are described as inclosing plane areas. The term "axis of the loop" refers to a straight line from the origin of the loop to its most distant part and is not to be confused with the mean electrical axis. In measuring angles in the frontal plane the conventional triaxial reference system was used. In the sagittal plane, angles were expressed similarly, with $\pm 180^\circ$ located anteriorly. The tracings in the sagittal plane were recorded as though viewed from the subjects' left.

*Analysis of this system indicate that the factors 1.2 and 1.7 should be $\sqrt{\frac{3}{2}}$ and $\sqrt{3}$, respectively.

†Auricular T records were not identified, since they were obscured in the QRS.

The axis of the P sĖ-loop is directed downward, slightly forward ($+95^\circ$ in its sagittal projection), and to the left ($+65^\circ$ in its frontal projection). The anterior surface of its inclosed area faces upward and to the left, being rotated counterclockwise on its longitudinal axis (as viewed from its distal end) about 45° from 12 o'clock. The P sĖ-loop is traced in a counterclockwise direction as viewed from the front. Its contour has a rather characteristic irregularity, with one or more large indentations. In a number of instances this resulted in a figure which might be described as resembling the outline of a mitten. The

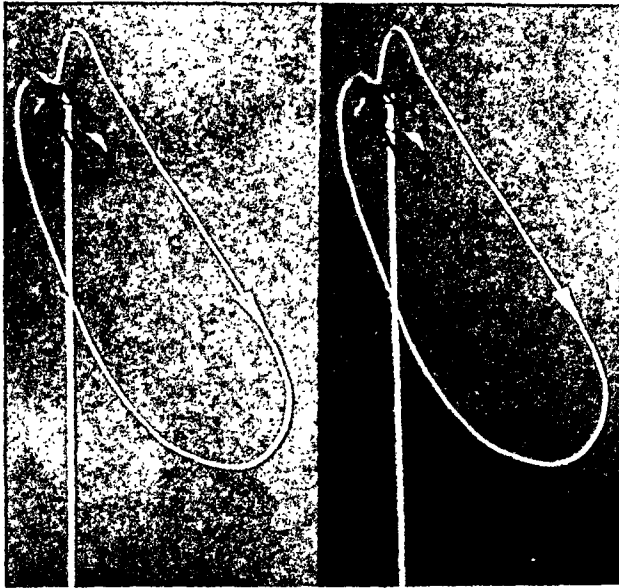


Fig. 2.*—Stereoscopic photographs of wire model representing an average normal vectorcardiogram as viewed from the front. The QRS sĖ-loop is in white, the P sĖ-loop is in gray, and the T sĖ-loop is in black in this and subsequent illustrations (except Fig. 4). Arrows denote direction in which sĖ-loops are traced.

*Stereoscopic effects are best obtained by placing a card between the two pictures and viewing from a distance of five to ten inches.

contour shows much greater change with respiration than does that of the QRS sĖ-loop or the T sĖ-loop, becoming narrower and more elongated on inspiration, with its axis becoming more nearly vertical (Fig. 4). At corresponding points in the respiratory cycle, similar contours recur. This may be seen by comparison of the P sĖ-loops in Figs. 3 and 6, which were recorded on the same individual at different times.

The axis of the QRS sĖ-loop is directed downward, forward ($+100^\circ$ in its sagittal projection), and to the left ($+65^\circ$ in its frontal projection). The anterior surface of this inclosed area, which is almost flat, faces upward and to the right, being rotated clockwise on its axis about 45 degrees. The loop is an ellipse-like figure whose width is less than one-third of its length. The QRS sĖ-loop is traced in a clockwise direction, as viewed from the front, slowly for a short distance from its origin, faster throughout the major portion, and slowly again near its terminus. Its contour exhibits no sudden irregular changes in direction (Fig. 5).

TABLE I. VECTORCARDIOGRAPHIC AXES OF QRS, T, AND P sE-LOOPS OF A GROUP OF NORMAL YOUNG MEN

VECTORCARDIOGRAPHIC AXES ON SAGITTAL PLANE												
VECTORCARDIOGRAPHIC AXES ON FRONTAL PLANE												
QRS			T		P		QRS		T		P	
ANGLE	LENGTH (mv.)		ANGLE	LENGTH (mv.)	ANGLE	LENGTH (mv.)	ANGLE	LENGTH (mv.)	ANGLE	LENGTH (mv.)	ANGLE	LENGTH (mv.)
Minimal	+30°	1.2	+10°	0.2	+20°	0.1	+95°	0.6	+115°	0.1	+20°	0.1
Maximal	+85°	4.6	+65°	0.8	+85°	0.5	+110°	4.7	+145°	0.9	+110°	0.5
Average	+65°	2.5	+45°	0.5	+65°	0.25	+100°	2.5	+125°	0.5	+95°	0.26

Normal Respiration

Minimal	+50°	1.05	+30°	0.14	+40°	0	+95°	0.9	+65°	0	+80°	0
Maximal	+90°	4.5	+80°	0.5	+90°	0.6	+110°	4.6	+130°	0.6	+115°	0.7
Average	+80°	2.8	+55°	0.3	+80°	0.3	+100°	2.8	+120°	0.3	+100°	0.35

Maximal Inspiration

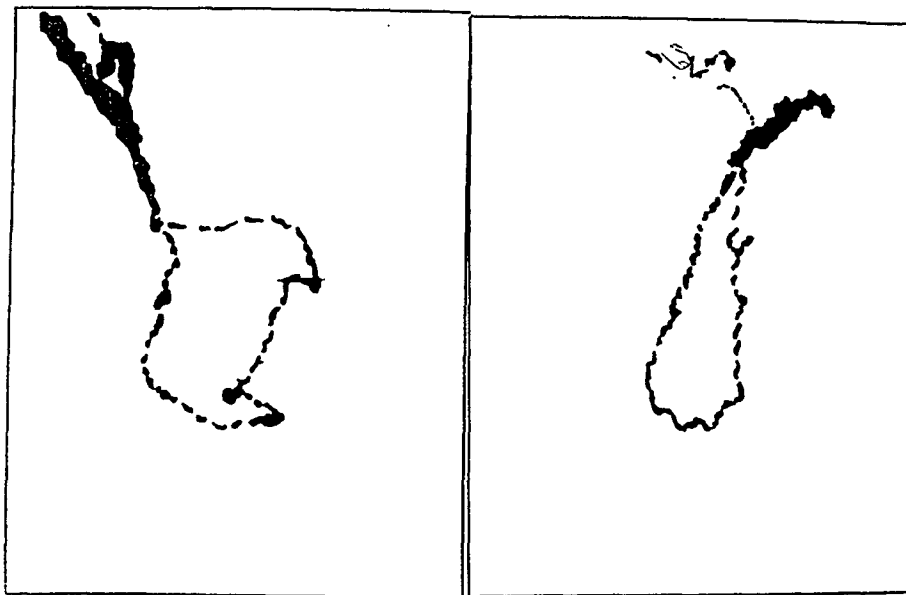


Fig. 3.—Records obtained simultaneously of frontal and sagittal projections of a normal P sE-loop.



Fig. 4.*—Effect of inspiration on a normal P sE-loop. The gray loop was obtained near the middle of the respiratory cycle and the white loop at deep inspiration.

*Stereoscopic effects are best obtained by placing a card between the two pictures and viewing from a distance of five to ten inches.

The axis of the T sE-loop is directed downward, forward ($+125^\circ$ in its sagittal projection), and to the left ($+45^\circ$ in its frontal projection). The anterior surface of its inclosed area faces upward and to the right, being rotated in a clockwise direction on its axis between 45° and 80 degrees. The loop is a very narrow ellipse-like figure. It is traced in a clockwise direction as viewed from the front, slowly in the efferent portion, faster in the afferent portion. In this part of the record there is an undulation which is especially apparent in the initial portion. The component waves are not regular either in form or frequency, and vary in pattern from cycle to cycle. It could not be established that these variations were related to respiration (Fig. 6).

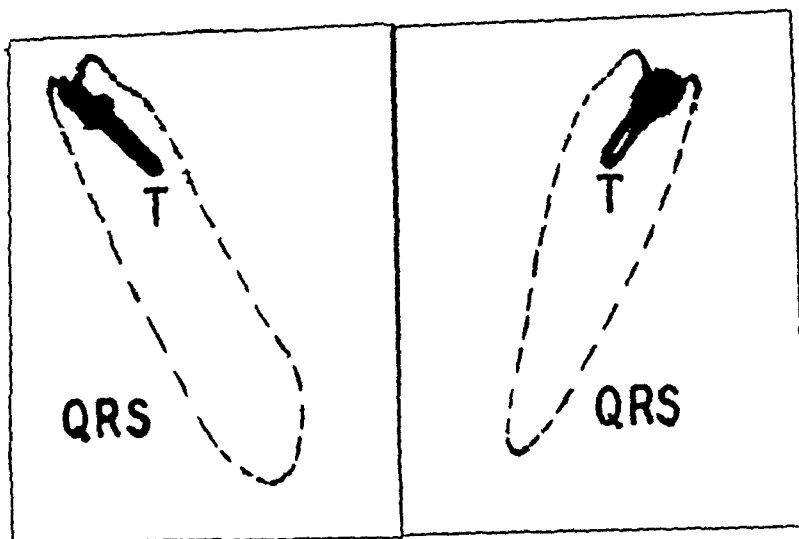


Fig. 5.—Records obtained simultaneously of frontal and sagittal projections of a normal QRS sÊ-loop.

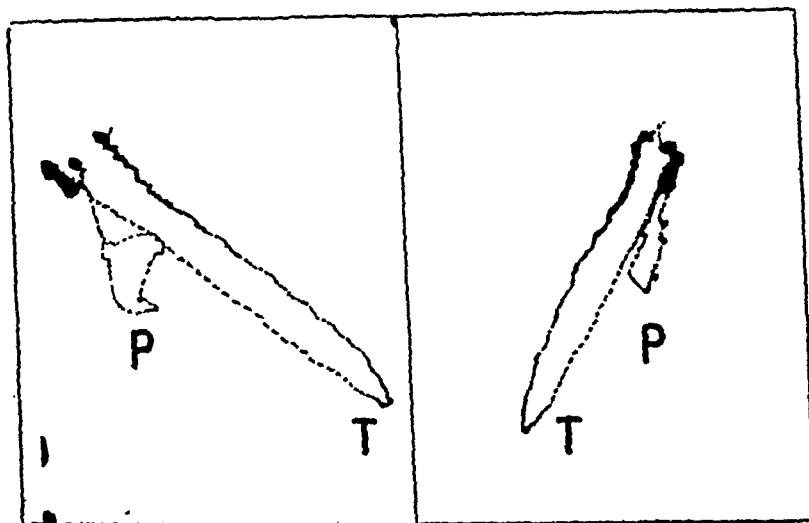


Fig. 6.—Records obtained simultaneously of frontal and sagittal projections of normal T and P sÊ-loops.

The approximate ratio of the axis lengths of the P, QRS, and T sÊ-loops to one another is 1:10:2, respectively.

Data obtained on this group of normal subjects are summarized in Tables I and II. To illustrate the extent of variation in the group, four models constructed from the records obtained are presented (Fig. 7).

Abnormal Subjects.—For purposes of comparison, three abnormal records are presented (Fig. 8):

1. *Left Bundle Branch Block in a Subject Receiving Digitalis* (Fig. 8,a): The QRS sÊ-loop had an irregular contour, with angular changes in direction.

TABLE II. DIRECTION OF TRACE OF QRS, T, AND P sÊ-LOOPS OF A GROUP OF NORMAL YOUNG MEN

COM- PLEX	FRONTAL PLANE			SAGITTAL PLANE		
	CLOCK- WISE	COUNTERCLOCK- WISE	LINE	CLOCK- WISE	COUNTERCLOCK- WISE	LINE
Normal Respiration						
QRS	11	5	0	0	16	0
T	13	1	2	0	13	3
P	2	11	2	3	9	4
Maximal Inspiration						
QRS	13	2	—	2	13	—
T	9	1	3	1	10	1
P	3	7	2	1	5	5

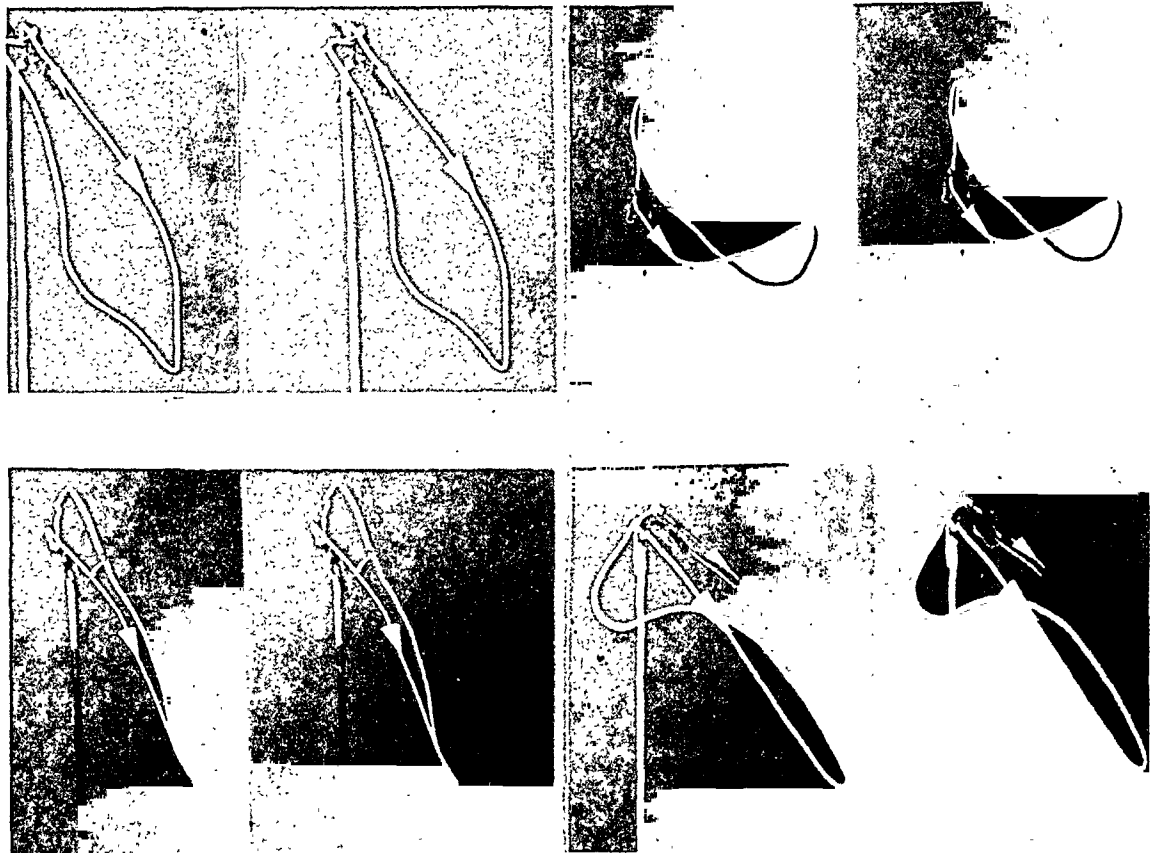


Fig. 7.*—Models of four normal vectorcardiograms.

*Stereoscopic effects are best obtained by placing a card between the two pictures and viewing from a distance of five to ten inches.

The projection of its axis on the frontal plane was at $+50^\circ$, on the sagittal plane at $+60$ degrees. The inclosed area faced upward, to the left, and slightly forward. The width of this area was almost as great as its length. The record was traced in a counterclockwise direction as viewed from the front, the initial part traced relatively slowly. Near the apex of the loop, and again near its most posterior point, there was sudden slowing in the tracing of the record. The portion of the record from the most posterior point to the beginning of the T sÊ-loop was traced forward, slightly downward, and to the right; ending above,

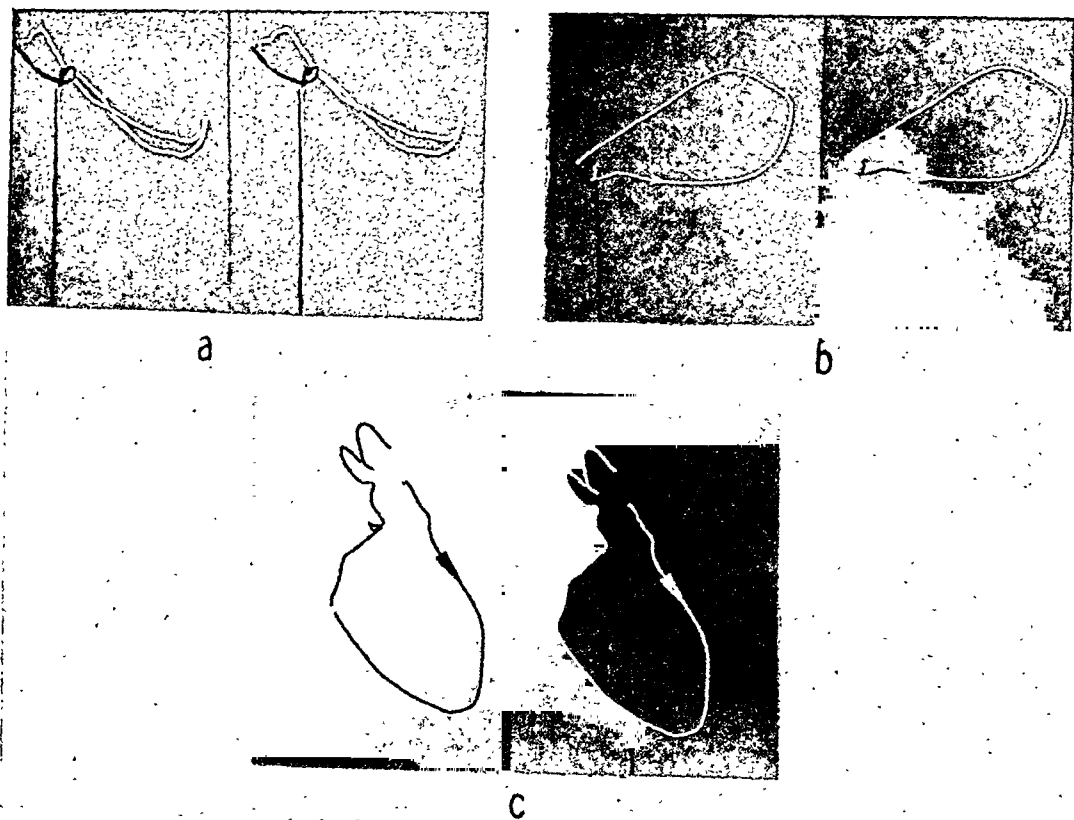


Fig. 8.*—QRS and T sÊ-loops of abnormal vectorcardiograms. *a*, Left bundle branch block. *b*, Left ventricular strain. *c*, Right bundle branch block.

*Stereoscopic effects are best obtained by placing a card between the two pictures and viewing from a distance of five to ten inches.

to the right of, and in front of its origin. At this location, there was an abrupt slowing in the tracing. From here the T sÊ-loop was directed forward initially, curving back to terminate near the point of origin of the QRS sÊ-loop. The inclosed area faced upward, slightly to the left, and slightly forward, its orientation being similar in this respect to that of the QRS sÊ-loop.

2. *Left Ventricular Strain* (Fig. 8,*b*): The QRS sÊ-loop had a smooth contour and was pear-shaped. The axis was directed slightly upward, very slightly backward, and to the left, its projection on the frontal plane being at -30° , and on the sagittal at about -60 degrees. The inclosed area faced almost directly

anterior, the loop being rotated clockwise on its anatomic axis about 20° from 12 o'clock. The record was traced downward to the right and forward for a short interval; then, abruptly changing direction, it was traced smoothly throughout the remainder in a counterclockwise direction as viewed from the front. Instead of returning to the point of origin, the loop terminated below, to the right, and in front of this point. Beginning at the end of the QRS and marked by a sudden slowing in the rate of tracing, the T sÊ-loop followed a slightly arched course with the convexity directed upward as it returned to a point near the origin of the QRS. The T sÊ-loop was very small, in comparison to the QRS sÊ-loop. Its entire length was about one-tenth the length of the axis of the QRS.

3. *Right Bundle Branch Block in a Subject Receiving Digitalis* (Fig. 8,c): The axis of the QRS sÊ-loop was directed downward and to the left, its projection on the frontal plane being at $+80^\circ$ and on the sagittal plane at $+90$ degrees. The portion of the loop from the origin to the apex was traced in a clockwise direction and had the appearance of a normal record to this point. From here the record was traced slowly, with numerous sharp irregularities in its form. This portion of the record terminated directly above its origin. The T sÊ-loop was inscribed in a clockwise direction as viewed from the front. Its contour was smooth, and its axis was directed backward and slightly to the left.

SUMMARY

1. A study of spatial vectorcardiograms has been made.
2. Data on normal vectorcardiograms of the P, QRS, and T sÊ-loops are presented, and a representative normal record is described.
3. Three abnormal vectorcardiograms are presented.

We wish to thank Dr. J. Leroy Kimball for his assistance in making this study possible.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die Manifeste Grosse der Potentialschwankungen im Menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. 150:275, 1913.
2. Mann, H.: A Method of Analyzing the Electrocardiogram, Arch. Int. Med. 25:283, 1920.
3. Wilson, F. N., Johnston, F. D., and Barker, P. S.: The Use of The Cathode-Ray Oscillograph in the Study of the Monocardiogram, J. Clin. Investigation 16:664, 1937.
4. Schellong, F.: Elektrokardiographische Diagnostik der Herzmuskelerkrankungen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. 48:288, 1936.
5. Sulzer, R., and Duchosal, P. W.: Principes de cardiovectographie, Cardiologia 9:106, 1945.
6. Sulzer, R., and Duchosal, P. W.: Le Cardiovectogramme normal, Helvet. physiol. acta 4:285, 1946.
7. Rochet, J., and Vastesaege, M.: Le Vectocardiogramme de l'homme normal, Trav. de Laboratoire de l'Inst. Solvay de Physiol. 29:17, 1944.
8. Vastesaege, M., and Rochet, J.: La Stereovectocardiographie et la stereovectocardiographie methodes cliniques d'étude de la repartition spatiale des potentiels cardiaques, Trav. de Laboratoire de l'Inst. Solvay de Physiol. 29:40, 1944.
9. Vastesaege, M., and Rochet, J.: Les Propriétés du Vectocardiogramme spatial de l'homme normal ses variations physiologiques, Trav. de Laboratoire de l'Inst. Solvay de Physiol. 29:55, 1944.
10. Wilson, F. N., Johnston, F. D., and Kossmann, C. E.: The Substitution of a Tetrahedron for the Einthoven Triangle, AM. HEART J. 33:594, 1947.
11. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, AM. HEART J. 16:14, 1938.
12. Conway, J. P., and Cronvich, J. A.: Observations on the Spatial Vectorcardiogram in Normal Man. Read before Southern Section, American Federation for Clinical Research, Jan. 26, 1948.

V. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN POSTERIOR INFARCTION

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WIDESPREAD interest in the electrocardiographic diagnosis of posterior infarction was awakened by the work of Pardee¹ on the Q wave in Lead III. In spite of the use of the Pardee criteria, with or without the various minor modifications subsequently proposed,²⁻¹⁰ the findings in the standard leads of many patients are not sufficiently decisive to clearly establish or positively exclude posterior infarction. The difficulty in the differentiation of the abnormal and normal Q₃ has been emphasized previously through a review of the literature and a study in this clinic of fifty subjects in which the final diagnosis was based chiefly upon the findings in the esophageal leads.¹¹ Although the pattern in the standard limb leads conformed with the Pardee criteria in forty-five of these subjects (including fourteen with a QS rather than a QR deflection in Lead III), a diagnosis of posterior infarction was established in twenty-four and was excluded in twenty-one. The standard leads of some of the subjects in the latter group were indistinguishable from those of proved cases of posterior infarction. A deep Q₃ and inverted T₃ simulating that associated with posterior infarction may be recorded as a normal variant when the heart is in horizontal, semihorizontal, or intermediate position. Under these conditions, the potential variations of the left ventricle are referred to the left arm and are recorded as a tall R wave and upright T wave in Lead aV_L, but as reciprocal downstrokes in Lead III, because of the fact that the galvanometric connection to the left arm in Lead III is the reverse of that in Lead aV_L.

A concomitant analysis of the findings in the unipolar left leg lead obtained on the same subjects confirmed previous reports of the occurrence of Q waves in this lead as a manifestation of posterior infarction.^{8,12-14} Lead aV_F revealed a Q wave which was more than 25 per cent of the amplitude of the succeeding R wave in twenty-two of the twenty-four subjects with proved posterior infarction, and in only three of the twenty-one subjects with a Pardee Q₃ (or prominent QS complex in Lead III), but without signs of posterior infarction in the esophageal leads. Thus, much closer agreement with the diagnosis established by esophageal leads was achieved in this series through an interpretation of Lead aV_F based on the Q/R ratio than through an interpretation of the standard leads based on the Pardee criteria.

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The experience with these cases brought out some, but not all of the errors that may occur in the interpretation of Lead aV_F . An incorrect diagnosis of posterior infarction could have been made in three cases from strict adherence to the Q/R ratio in Lead aV_F . The low voltage of the QRS complex in Lead aV_F of two of these cases with Q/R ratios over 25 per cent indicated a need for caution in the interpretation of the findings in this lead when the voltage of the QRS complex does not exceed 0.5 millivolt. The experience with the third case emphasized the importance of interpreting the findings in Lead aV_F in the light of those in other unipolar leads rather than as an isolated entity. A record of Lead aV_F , taken in the recumbent position, revealed a deep QS complex, consistent with the pattern of posterior infarction, but actually due to reference of the potential variations of the right ventricle to the left leg, as indicated by (1) its resemblance to the QS complex of Lead V_1 , (2) its replacement by an RSR' complex of transitional type when Lead aV_F was repeated with the patient in the erect posture, and (3) the absence of abnormal Q waves in esophageal leads at the ventricular level. A known healed posterior infarct was not diagnosable from Lead aV_F in two cases, apparently because the lesion, judging from the findings in the esophageal leads, was small and confined to the posterobasal wall near the atrial margin.

Goldberger¹⁵ reported that a Q wave in Lead aV_F which had a duration of 0.04 second and an amplitude 60 per cent of that of the succeeding R wave or 40 per cent of that of the entire QRS complex was diagnostic of posterior infarction. Goldberger's measurements of the duration of the Q wave are not comparable with ours, since his were made from the onset of the QRS complex to the point where the upstroke of the R wave returned to the base line, whereas ours were made from the onset to the nadir of the Q wave. Upon application of his criterion of Q/R ratio to our former series, it is noteworthy that two of the uninfarcted controls had Q/R ratios over 60 per cent, whereas four of the cases of posterior infarction had ratios below 60 per cent and two others had borderline values of 60 per cent. Thus, his more rigid criterion eliminates some of the cases of posterior infarction and fails to exclude some of the uninfarcted controls.

The incidence of diagnostic signs in Lead aV_F was high in our previously reported series, particularly when one considers that the posterior infarct was healed in twenty of the twenty-four cases. The favorable results could be explained in part by the fact that the cases did not represent a consecutive series, but rather, a selected group, studied because of a pattern in the standard leads that conformed with the criteria of Pardee. This method of selection favored inclusion of cases likely to have diagnostic signs in Lead aV_F , since posterior infarction that is responsible for a Pardee Q_3 should also be manifested by an abnormal Q wave in Lead aV_F .¹¹ The latter reflects abnormal initial negativity of the left leg and is prone to occur as a manifestation of posterior infarction when the heart is in an intermediate to vertical position favorable to the transmission of negative cavity potentials through the infarcted posterior wall to the diaphragm and thence to the left leg. Moreover, this method of selection tended to exclude most of the cases of posterior infarction unlikely to have

diagnostic signs in Lead aV_F because of a semihorizontal to horizontal cardiac position. Under these circumstances, the potential variations of the left leg are transmitted chiefly from the posteroinferior wall of the right ventricle and are characteristically recorded as an RS deflection in Lead aV_F . Since this RS pattern generally carries over into Lead III, most cases of posterior infarction, undetectable from Lead aV_F because of horizontal position, were automatically excluded from our former series. On the other hand, a few cases with an RS pattern in Lead aV_F and a tall R wave in Lead aV_L , due to semihorizontal to horizontal position, will display a Pardee Q_s , because of the fact that the small initial positive potential of the left leg is relatively negative in comparison with the marked positivity of the left arm. Such a pattern may be encountered as a coincidence in posterior infarction, but is of no diagnostic significance, since it also occurs in the absence of infarction.

In view of the foregoing considerations, there appeared to be a need for an evaluation of Lead aV_F in the diagnosis of posterior infarction based upon the findings in a large consecutive series in which the presence of posterior infarction was established by autopsy. In 110 of our 161 cases,¹⁶ post-mortem examination disclosed an infarct extending one-third or more of the length of the posterior wall of the left ventricle. This does not imply that the infarct involved one-third or more of the cubical area of the posterior wall, since in many cases it was limited to the subendocardial layer and/or a portion of the posterior wall between the junction with the septum and lateral wall. In this communication an analysis will be presented of the findings in Lead aV_F in the entire group of 110 cases and the correlation of electrocardiographic and pathologic findings will be exemplified by detailed reports of twenty-one cases and a tabular summary of sixteen cases.

CASE REPORTS

CASE 87.—A 60-year-old woman was stricken with repeated vomiting on the evening of March 14, 1945, which was not accompanied by thoracic or abdominal pain. Early the next morning she was brought to the hospital in shock with a blood pressure of 45/0. Examination after recovery from shock revealed a harsh systolic murmur, maximal at the apex, but audible over the entire precordium. On March 19 a pericardial friction rub was heard. The patient was stuporous and irrational throughout hospitalization and died on April 6.

Electrocardiographic Findings.—Electrocardiograms selected from a series taken during her hospital course are reproduced in Fig. 1. Digitalis, 0.3 Gm., was given before the first electrocardiogram and was then discontinued. After the tracing of March 22, digitalis was reinstituted and a total of 1.2 Gm. was given up until March 26, when it was again withdrawn. The abnormal QS complex and the RS-T displacement in Leads aV_F , II, and III on March 16 were diagnostic of recent posterior infarction. The digitalis dosage was insufficient to account for the marked RS-T depression in Leads V_1 through V_6 , leaving two possibilities for consideration, namely: (1) a reciprocal effect from the acute posterior infarct, and (2) a direct effect from continuation of the lesion into the subendocardial portion of the anterolateral wall. The current of injury associated with recent myocardial infarction is manifested indirectly by elevation of the RS-T segment in unipolar leads facing the epicardial surface of the infarcted wall and by depression of the RS-T segment in unipolar leads facing the endocardial surface. Precordial leads characteristically show acute depression of the RS-T segment in recent posterior infarction, since they face the endocardial surface of the lesion. The degree of depression in precordial leads may exceed the elevation in Lead aV_F because of the closer proximity of the former to the infarct. Since the displacement of the RS-T segment in the precordial leads of these tracings could represent

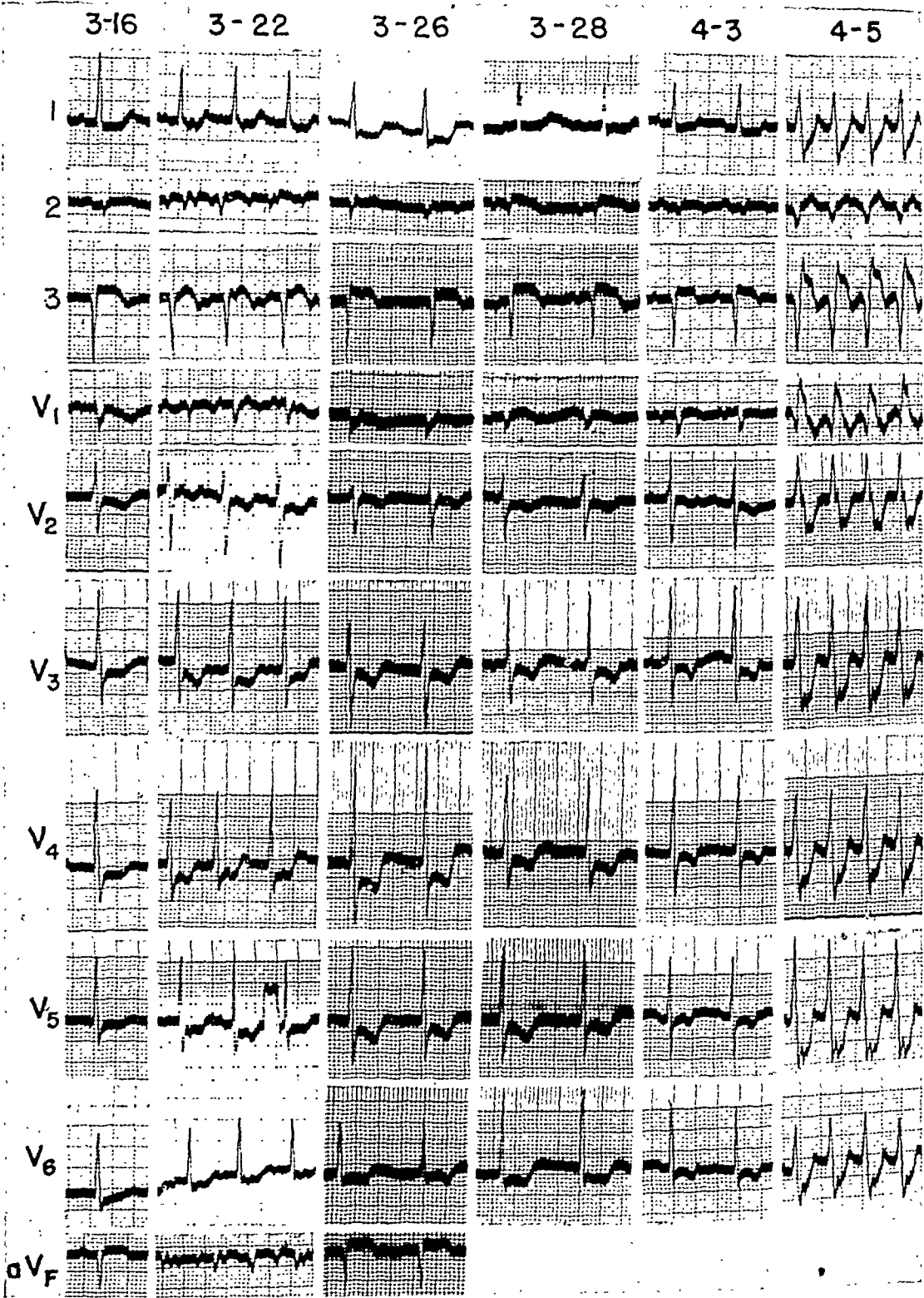


Fig. 1.—Serial electrocardiograms in Case 87.

a reciprocal effect of the recent posterior infarct, the additional diagnosis of extension into the subendocardial portion of the anterolateral wall was unjustified. A nodal tachycardia with variable A-V block, chiefly 2:1, was present on March 22, and a wandering pacemaker, chiefly lower nodal, was found on March 26. The pacemaker shifted to the upper portion of the A-V node on March 28 and reverted to the sinus node at the next tracing. The increased upward displacement of the RS-T junction in Lead aV_F and the depression in Leads V_1 through V_6 on March 26 were suggestive of further injury to the subepicardial portion of the posterior wall, but might have been due merely to the superimposed effects of digitalis. However, in Lead V_1 , the only precordial lead that consistently reflected the potential variations of the right ventricle and right side of the septum, the RS-T segment underwent a significant change, indicative of myocardial injury and independent of digitalis. The depression of the RS-T segment in Lead V_1 on March 16 represented

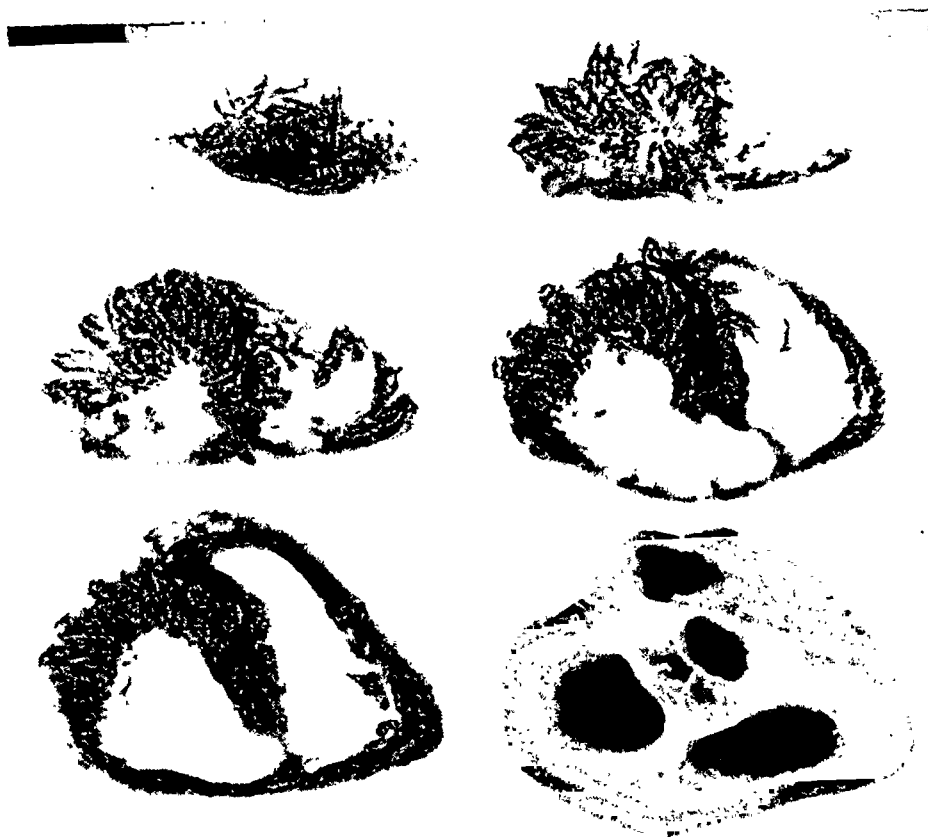


Fig. 2.—Roentgenogram of the injected heart in Case 87, showing large infarct of the posterobasal walls of the left and right ventricle and the posterior one-half of the septum with perforation of the latter at the base.

a typical reciprocal effect from posterior infarction and resembled that recorded in leads over the anterior wall of the left ventricle, such as Lead V_3 . The dome-like elevation of the RS-T segment in Lead V_1 on March 26, March 28, and April 3 resembled that in Lead aV_F , which reflected the potential variations of the infarcted posterior wall of the left ventricle. The following possible explanations for the change in the pattern of the RS-T segment in Lead V_1 were considered: extension of the infarct into the septum, infarction of the right ventricle, pericarditis, and shift of cardiac position so as to facilitate transmission of the potential variations of the posterior wall of the left ventricle into the right precordium. The latter was excluded by absence of concomitant change in the QRS pattern. Pericarditis was unlikely because of the localization to a single lead. Extension of the infarct into the septum was considered much more likely than extension into the

right ventricle. The final tracing showed apparent flutter waves in Leads V_1 and III, a 2:1 A-V ratio, with regularly spaced QRS complexes indicative of right bundle branch block. The question arose as to whether the terminal right bundle branch block was due merely to the ventricular rate of 176 or whether it was a manifestation of septal infarction. The prominent Q wave, preceding the late R wave in Lead V_1 , pointed strongly toward infarction of the septum,¹⁷ but it is possible that the initial R wave customarily associated with right bundle branch block was obliterated by the flutter wave rather than as a result of septal infarction. It is noteworthy that deep Q waves persisted in Leads II and III in the face of the right bundle branch block. The remaining precordial leads showed an initial R wave and a relatively early intrinsicoid deflection, from which it was concluded that the infarct had not continued into the anterolateral wall of the left ventricle.

Pathologic Findings.—The heart weighed 400 grams and exhibited a large, organizing, transmural posteroseptal infarct, which caused marked thinning of the basal two-thirds of the posterior wall of the left ventricle and the posterior one-half of the interventricular septum, as evident in the roentgenogram (Fig. 2). In the posterobasal portion of the septum, there was a perforation 3.0 cm. in diameter which had sharp edges and was believed to have been present for a number of days. The infarct continued across the septum to involve the posterobasal two-thirds of the right ventricle. The anterior walls of both ventricles and the anterior half of the septum were intact. The extensive transmural posterior infarct adequately accounted for the QS complex and RS-T pattern in Lead aV_F , but the alternative possibility that the pattern in Lead aV_F was a manifestation of the septal portion of the infarct in a horizontally placed heart was not definitely excluded. The RS-T depression and T-wave inversion in Leads V_2 through V_6 were apparently reciprocal to the posterior infarct. Although the lesion extended well into the posterolateral wall at the base, there were no abnormalities in the initial deflection in Lead V_6 . The developing RS-T elevation in Lead V_1 and the terminal right bundle branch block were probably referable to the infarction of the posterior half of the interventricular septum. In view of the complete destruction and perforation of the posterobasal portion of the septum, it is remarkable that the P-R and QRS intervals were normal in the tracing of April 3, taken three days before death. The nodal tachycardia may have represented an irritative phenomenon secondary to the septal infarction. There was no gross evidence of infarction of the atria to account for the terminal flutter, but adequate microscopic study was not made.

CASE 88.—A 69-year-old man had had hypertension for several years, but was otherwise well until April 4, 1944, when he was seized with severe retrosternal pain followed by loss of consciousness. He was admitted to the hospital in shock one hour later and remained in collapse until his death on April 7, 1944. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained about five hours after the onset of symptoms is reproduced in Fig. 3 along with two subsequent tracings. Complete A-V block was present throughout. The form of the QRS complex suggested a nodal pacemaker. Although the QR complex in Lead aV_F was not, in itself, diagnostic, the extreme RS-T elevation in Lead aV_F and marked reciprocal depression in aV_L were typical of recent posterior infarction. The tall, upright T waves in Leads aV_F , II, and III of the first tracing constituted a recognized early finding¹⁸ and the subsequent reduction in voltage and inversion of the terminal portion of the T waves represented a characteristic evolution. The first phase of the QRS complex was upright in all precordial leads and was 0.5 mm. in amplitude in Lead V_1 , increased to 2.0 mm. in Lead V_2 , then decreased to .05 mm. in Lead V_3 . The abnormal reduction in the R wave of Lead V_3 , together with the elevation of the RS-T junction and convexly upward RS-T segment in the first four precordial leads, raised the question of coexistent anteroseptal infarction. A recent pericarditis over the anterior wall in association with an old, healed anteroseptal infarction was also considered. The suspicion of anteroseptal infarction was temporarily dropped after the record of April 6, which revealed a normal QRS-T pattern in the precordial leads, but was resumed after the last tracing because of the reduction in the voltage of the R wave in the first four precordial leads, together with recurrence of RS-T elevation in Leads V_1 through V_3 . The inversion of the T waves in Leads V_5 and V_6 , in view of the absence of Q waves from these leads, suggested an outlying zone of ischemia in the lateral wall of the left ventricle.

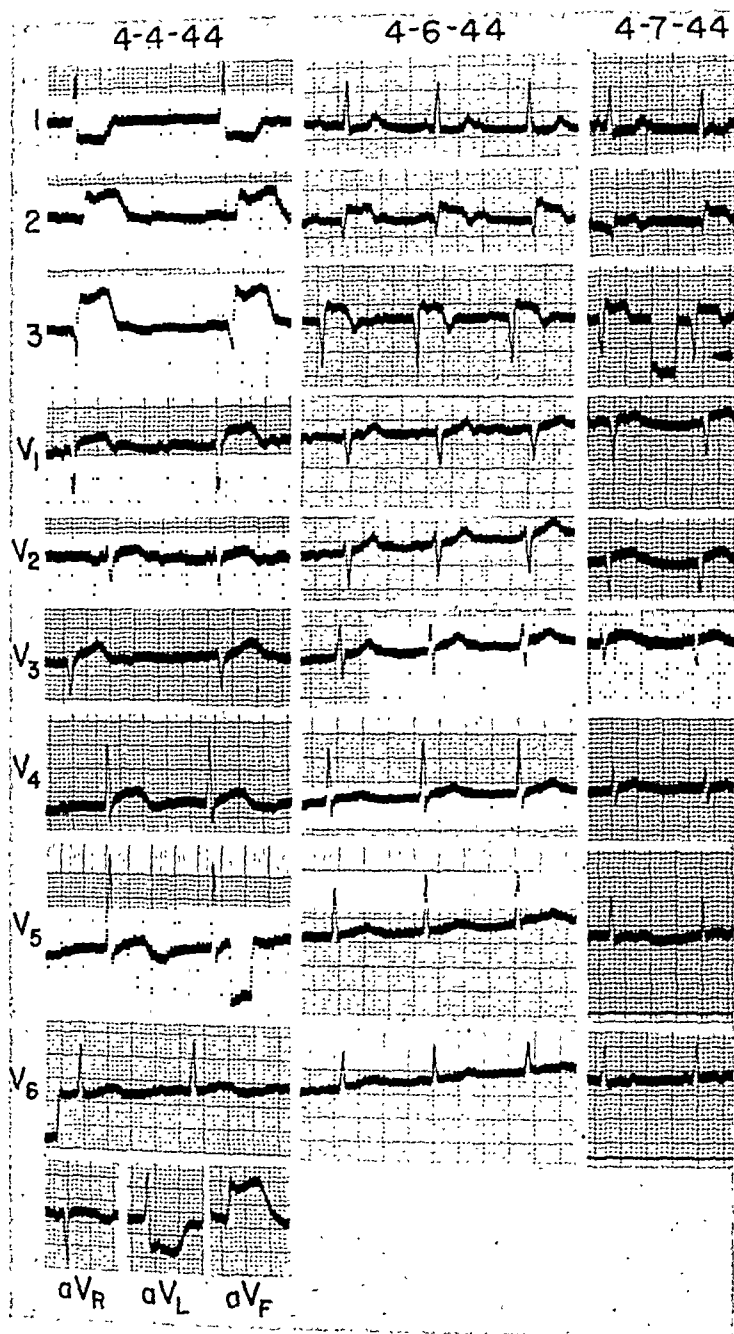


Fig. 3.

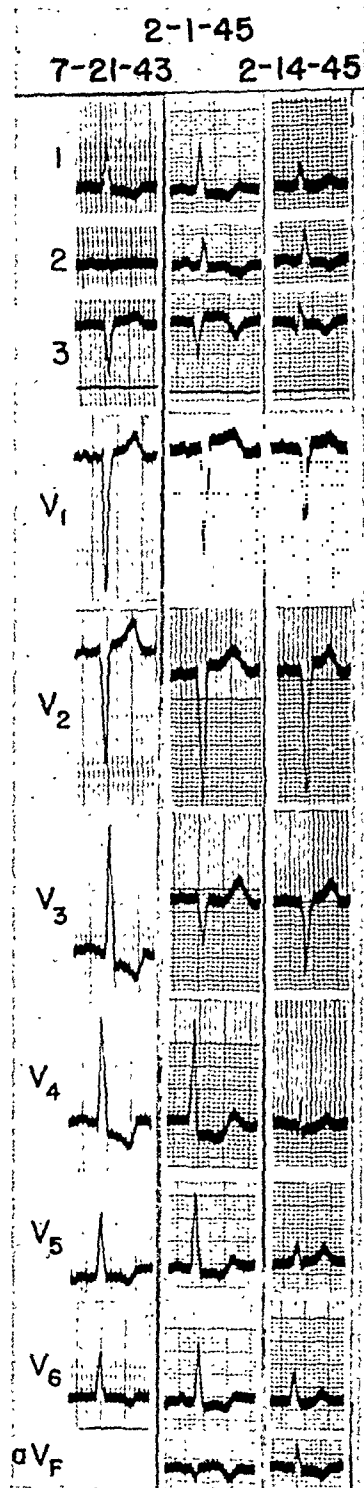


Fig. 4.

Fig. 3.—Serial electrocardiograms in Case 88.

Fig. 4.—Serial electrocardiograms in Case 89 before and after the development of posterior infarction.

Pathologic Findings.—The heart weighed 525 grams and exhibited a massive transmural infarct of the entire posterior surface of the left and right ventricles from base to apex, as well as the posterior half of the interventricular septum, occupying essentially the same position in the entire length of the posterior wall as the lesion in the third, fourth, and fifth segments of Fig. 2. A fibrinous pericarditis was found in the area of infarction, but the epicardium and myocardium of the anterior wall were negative. The relatively low Q/R ratio in Lead aV_F of the first tracing was probably due to the brief interval of five hours between the onset of symptoms and the recording of the electrocardiogram. Unfortunately, Lead aV_F was not repeated, but, judging from the changes in the initial deflection in Leads II and III, it would probably have shown a much deeper Q wave and larger Q/R ratio. The extension of the infarct into the posterior portion of the septum was apparently responsible for the complete A-V block. The infarct extended sufficiently into the posterolateral wall to explain the T-wave changes in Leads V₅ and V₆. Since the first three precordial leads reflected the potential variations of the right ventricle and right side of the septum, the reduction in the R wave and the RS-T elevation in these leads on April 7 could be attributed to the septal infarction, whereas the small RS complex in Lead V₄ might have represented a transitional zonal phenomenon. Since the RS-T displacement in the first tracing extended into left ventricular Lead V₄, it could not be explained by the septal infarction. It is possible that there was a transient acute injury to the anterior wall, associated with the shock, but not progressing to the stage of infarction.

CASE 89.—A 60-year-old diabetic woman gave a history of slowly increasing exertional dyspnea since 1937 and typical angina pectoris of gradually increasing severity since 1941. On Feb. 1, 1945, she was awakened by a much more severe constrictive retrosternal pain and was admitted to the hospital ten hours later. Hospital course was complicated by bronchopneumonia and death occurred on the thirty-second day.

Electrocardiographic Findings.—Electrocardiograms before and after the final episode are reproduced in Fig. 4. The tracing of July 21, 1943, was obtained eight days after the withdrawal of digitalis. The minute R wave and deep S wave in precordial leads over the right ventricle and the tall R wave with slightly delayed peak in leads over the left ventricle were similar to those in six previous tracings and were interpreted as evidence of left ventricular hypertrophy. The depressed RS-T junction and inverted T waves of Leads V₃ through V₆ were probably in part associated with left ventricular hypertrophy and in part a remnant of digitalis action. A QS complex seemed to be present in Lead III on July 21, 1943, but a distinct initial R wave was found in other tracings during the preceding and the subsequent years. Through an oversight, Lead aV_F was not obtained until February, 1945. No cardiac glycosides were administered during the month preceding the last two tracings. The QRS complexes of the standard leads on Feb. 1, 1945, did not differ significantly from those on July 21, 1943, but the appearance of a coved, negative T₃ and a reciprocally depressed RS-T segment in Lead I strongly suggested recent posterior infarction. The broad, slurred QS deflection and classical T wave in Lead aV_F established the diagnosis. Right ventricular Leads V₁ and V₂ showed virtual disappearance of the previous minute initial R wave, whereas left ventricular Leads V₄ through V₆ showed no change in the QRS complex, but a significant increase in depression of the RS-T segment. This was more likely a reciprocal effect from the recent posterior infarct than a result of extension subendocardially into the anterolateral wall. In Lead aV_F, on February 14, the Q wave had decreased to 1.0 mm. and an R wave 4.0 mm. tall had appeared. The T wave was still inverted, but the RS-T junction had become isoelectric. The altered pattern in Lead aV_F was carried over into Lead III. Three alternative explanations were considered for the change from a QS to a borderline QR pattern no longer diagnostic of infarction: (1) The entire thickness of the posterior wall may have failed to respond to the activating impulse on February 1, resulting in the registration of a QS complex in Lead aV_F, and the subepicardial portion may have recovered subsequently, resulting in the development of an R wave at the expense of the Q wave. (2) A permanent small transmural infarct may have been localized to a portion of the posterior wall and the position of the heart in reference to the diaphragm, on February 1, may have been favorable to the transmission of the potential variations of the infarcted area to the left leg, whereas the position may have changed in the intervening two weeks so as to facilitate

transmission of the potential variations from an outlying ischemic zone. (3) The findings on February 1 may have been referable to septal infarction in a horizontally placed heart and the subsequent change may have been due to shift into intermediate position. A positive differentiation between these three alternatives was not made, because of failure to repeat tracings in different postures and respiratory phases. The striking reduction in the voltage of the R wave in Leads V_4 through V_6 and in Lead I of the tracing of February 14 could not have been due to a technical error, since the standardization curve in each of these leads showed a deflection of 1.0 cm. in response to a potential difference of 1.0 millivolt. Patchy infarction of the antero-lateral wall may decrease the height of the R wave in these leads, but was considered very unlikely in this case because of the absence of associated changes in the RS-T segment and T wave. The disappearance of the RS-T displacement and increased height of the T wave in Leads V_4 through V_6 and Lead I constituted the expected findings in the evolution of a recent posterior infarction. The reduction in the voltage of the R wave was concurrent with the development



Fig. 5.—Roentgenogram of the injected heart in Case 89, showing position of posteroseptal infarct.

of bronchopneumonia complicated by left pleural effusion and was attributed to the appearance of an exudate in the intervening lung and pleura. Such an explanation would also account for the lack of significant changes in the voltage of the QRS complex in Leads V_1 through V_3 , which lay to the right of the pulmonary lesion.

Pathologic Findings.—The heart weighed 514 grams and showed an organizing posterior infarct occupying the areas outlined in Fig. 5. The infarct involved the subendocardial one-third of the posterior wall from apex to base, continuing for a short distance into the left side of the septum and extending into the subepicardial zone in the middle third of the posterior wall. Reference of the potential variations of the third and fourth segments to the leg might have accounted for the original QS pattern in Lead aV_F , and a subsequent shift to bring either more apical or basal portions of the posterior wall into closer opposition to the diaphragm might have

explained the later QR pattern. The other alternatives were also compatible with the autopsy findings. Since there was no evidence of infarction of the anterior or lateral wall, the RS-T depression on February 1 was evidently a reciprocal effect of the recent posterior infarct, and the reduction in the voltage of the R wave in Leads V_4 through V_6 on February 21 was of extracardiac origin. Although septal infarction may be manifested by QS complexes in right ventricular leads, the virtual disappearance of the initial R waves in Leads V_1 and V_2 of the last two tracings was probably unrelated to the small lesion limited to the left side of the posterior third of the septum.

CASE 90.—A 59-year-old man was awakened by severe, choking retrosternal pain, which necessitated hospital admission three hours later. He had had a similar attack one year pre-

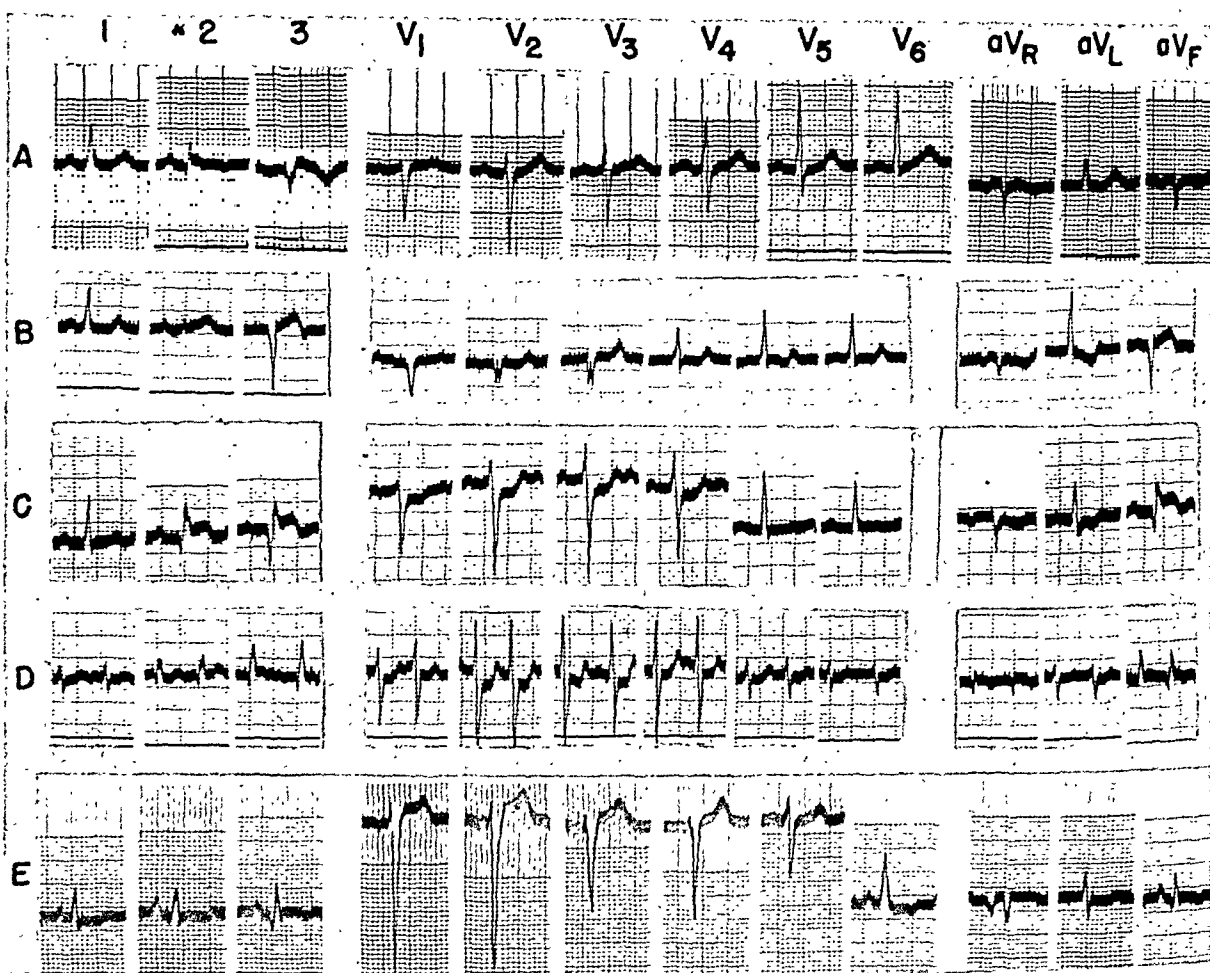


Fig. 6.—Electrocardiographic findings in recent posterior infarction. A, Case 90; B, Case 91; C, Case 92; D, Case 93; and E, Case 94.

viously, which lasted only one and one-half hours. Death occurred eighteen hours after admission. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained eleven hours after the onset of the pain is reproduced in Fig. 6, A. The abnormal Q_2 and QS complex in Lead III, together with elevation of the RS-T segment in Leads II and III and inversion of the T waves, were quite typical of posterior infarction, and the diagnosis was confirmed by the abnormal QS complex and inverted T wave of Lead aV_F . All precordial leads were within normal limits. The only other noteworthy finding was a shifting pacemaker from the sinus to the A-V node.

Pathologic Findings.—The heart weighed 524 grams and displayed a transmural infarct of the posterior one-third of the interventricular septum and the adjacent posterior septal portions of the basal three-fifths of the left and right ventricles, as brought out in Fig. 7. Microscopic examination showed that the lesion was transmural and consisted of an old healed infarct of the subendocardial one-half and a recent infarction of the remainder of the wall. Although a cardiac position favorable to the predominant transmission of the potential variations of the epicardium covering the transmural infarct of the posterior wall to the left leg could have accounted for the QS pattern in Lead aV_F , a late R wave larger than the notch near the end of the QRS complex would have been expected from activation of the surrounding uninfarcted portion of the free wall. For this reason, it was necessary to consider the alternative possibility that the heart was in semihorizontal position and that the septal portion of the infarct was responsible for the findings in Lead aV_F .



Fig. 7.—Roentgenogram of the injected heart in Case 90.

CASE 91.—A previously healthy 81-year-old man was suddenly stricken with retrosternal pain and dyspnea three weeks before hospital admission. He was finally brought to the hospital because of the development of anuria and circulatory collapse. No cardiac glycosides were given. Death occurred on the fourth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained two hours after admission is reproduced in Fig. 6,B. The tall R wave in Lead aV_L coupled with the deep downstroke in Lead aV_F raised the question of horizontal position with reference of the potential variations of the right ventricle to the left leg to account for the findings in Lead aV_F . However, close scrutiny of the ventricular complex in Lead aV_F revealed a small late R wave, which could not have been derived from the right ventricle. Thus, the QR complex in Lead aV_F was believed to be

of left ventricular origin, and was considered diagnostic of posterior infarction, particularly in view of the 0.05 second interval between the onset and nadir of the Q wave. Elevation of the RS-T segment was attributed to recent infarction, inasmuch as digitalis had been excluded by the history. The findings in Lead III duplicated those in Lead aV_F. The Q wave was absent from Lead II, but the slight elevation and straightening of the RS-T segment in this lead was somewhat suggestive of recent infarction. In Leads V₁ and V₂ there was a slurred to W-shaped QRS complex and in Lead V₃ there was an initial R wave of 1.0 mm. followed by a notched S wave. A posterior infarction tends to reduce forces that are antagonistic to those which produce the R wave in precordial leads. Hence, in uncomplicated posterior infarction there is a tendency toward exaggeration of the R wave in precordial leads. For this reason, the initial Q wave in Leads V₁ and V₂ and the minute R wave in Lead V₃ were attributed to involvement of the septum and adjoining anterior wall. The pattern of the RS-T segment in these leads was more in keeping with an old lesion. Thus, a diagnosis was made of a recent posterior and old, healed anteroseptal infarct.

Pathologic Findings.—The heart weighed 400 grams and displayed a recent infarct of the posterior wall adjacent to the septum, occupying a position almost identical with the subendocardial portion of the infarct in Case 89 (Fig. 5). Microscopic sections showed an organizing infarct, extending through the subendocardial three-fourths of the posteroseptal wall. In addition there was an old, completely healed infarct, occupying the subendocardial one-half of the anteroseptal wall and extending into the left side of the anterior half of the septum. Although the anteroseptal infarct was localized to the apical one-half of the left ventricle, it presumably caused sufficient reduction in forces produced by septal activation to account for the absence of the initial R wave in Leads V₁ and V₂ and the minute initial upright deflection in Lead V₃. There was sufficient patchy fibrosis at the apex to account for the notching or slurring of the R wave in Leads V₄ and V₆. The abnormally deep and prolonged Q wave and subsequent small R wave of Lead aV_F could be correlated with the more recent infarct of the subendocardial three-quarters of the posterior wall.

CASE 92.—A 63-year-old man was admitted to the hospital six hours after the onset of a constricting precordial pain, which radiated into both arms. There were several recurrences of pain during hospitalization. He died in sleep on the ninth day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the seventh hospital day is reproduced in Fig. 6,C. The QRS interval, as measured in Lead aV_F, was 0.12 or 0.02 second greater than in the precordial leads. The abnormal QR complex, elevated RS-T junction, and monophasic upright T wave in Lead aV_F were typical of recent posterior infarction and carried over into Leads II and III. The 2.0 mm. depression of the RS-T segment in the first four precordial leads and the 1.0 mm. depression in Lead aV_L were attributed to the acute posterior infarction rather than to an independent lesion of the subendocardial layer of the anterolateral wall, because of the reciprocal relationship with the findings in Lead aV_F in serial tracings. An electrocardiogram obtained on the second hospital day (five days prior to that reproduced in Fig. 6,C) showed a similar QRS pattern in Lead aV_F and the precordial leads, but showed significant differences in the RS-T segments and T waves. Lead aV_F displayed only a slight RS-T elevation and a deeply inverted T wave, whereas the first three precordial leads showed an isoelectric RS-T segment and tall, erect T waves. The increased upward displacement of the RS-T segment in Leads aV_F, II, and III and the concomitantly developing depression in Leads V₁, V₂, and V₃ during the intervening five days were referable to further acute injury to the subepicardial layer of the posterior wall, due either to extension of the posterior infarct or overlying pericarditis.

Pathologic Findings.—The heart weighed 545 grams and revealed a recent transmural infarct involving the entire posterior wall except at the apex and extending into the posterior portion of the basal third of the septum, as outlined in Fig. 8. Death was due to rupture of the posterior wall in the basilar segment. Microscopic sections showed an infarct of about ten days

in age and a more recent extension in the two basilar segments. These findings corresponded closely with the position of the infarct as judged by the abnormal QR pattern in Leads aV_F, II, and III and the recent extension as predicted from the increased elevation of the RS-T segment in Lead aV_F together with the reciprocal depression, developing in the first three precordial leads.

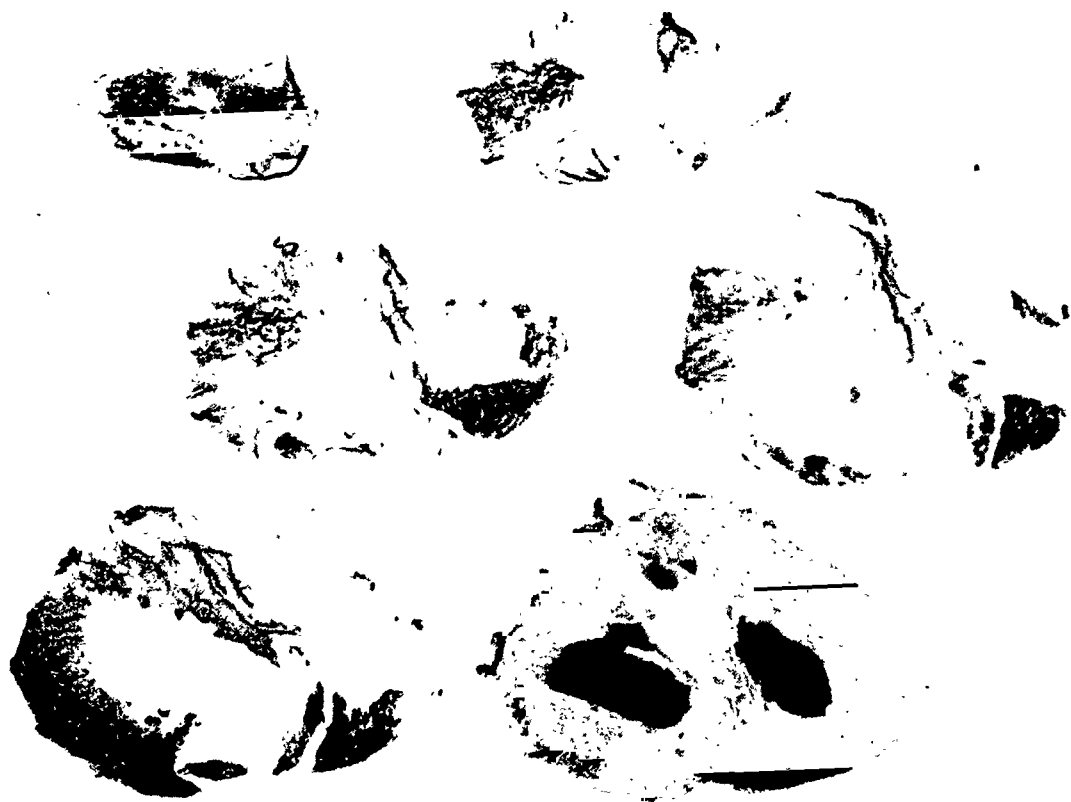


Fig. 8.—Roentgenogram of the injected heart in Case 92.

CASE 93.—A 70-year-old man gave a history of an attack of severe retrosternal pain twenty-one years previously, from which he made a complete recovery. He had had recurrent bronchitis for nine years, but had no further cardiac symptoms until three days before admission to the hospital, when he was suddenly seized with a severe choking sensation accompanied by orthopnea. Death occurred on the second hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained after the administration of 1.2 mg. of Cedilanid and seven hours before death is reproduced in Fig. 6, D. Auricular fibrillation was present with a ventricular rate of approximately 150 per minute. The standard leads showed a right axis deviation with a slurred RSR' complex in Lead II and a QR complex in Lead III, which was not diagnostic of either recent or old myocardial infarction. On the other hand, Lead aV_F showed a Q wave of 0.02 second duration that ranged from 1.0 to 3.0 mm. in depth and varied from 15 to 50 per cent of the amplitude of the succeeding R wave. The Q/R ratio, together with the slurring and slight prolongation of the ascending limb of the R wave, the slight elevation of the RS-T junction, and the inversion of the T wave, was strongly suggestive, though not pathognomonic, of posterior infarction. All precordial leads revealed an RS complex which maintained a fairly constant ratio throughout, but decreased in voltage as

the electrode was moved into the axilla. The relatively constant R/S relationship suggested a broad transitional zone, as a result of parallelism between the long axis of the septum and the pathway of the electrode from precordial Position 2 to Position 6. The rather striking depression of the RS-T segment in the first four precordial leads may have been due in part to Cedilanid, but was probably not produced exclusively by this glycoside, since the Q-T interval was at the upper limits of normal. When considered in the light of the findings in Lead aV_F, the reciprocal effect of a recent posterior infarction was regarded as a factor in the depression of the RS-T segment.

Pathologic Findings.—The heart weighed 469 grams and exhibited an old healed infarct of the subendocardial three-quarters of the posterior wall, as is evident in Fig. 9. A hemorrhagic discoloration was found in the posterolateral aspect of the apical segment and represented a recent extension of the old posterior infarct. Thus, the findings in Lead aV_F gave a better repre-



Fig. 9.—Roentgenogram of the injected heart in Case 93.

sentation of the posterior infarct than those in the standard leads. The recent extension into the posterolateral wall of the apex was probably in part responsible for the depression of the RS-T segment in the first four precordial leads, but produced no direct signs in Lead V₅, V₆, or aV_L, probably because these leads did not reflect the potential variations of the lateral aspect of the left ventricle.

CASE 94.—A 58-year-old man had had exertional and paroxysmal nocturnal dyspnea for two years and repeated attacks of severe constrictive retrosternal pain during the four months preceding hospital admission. He was brought to the hospital because of a particularly severe attack of retrosternal pain complicated by cardiac failure and died suddenly on the fourth hospital day.

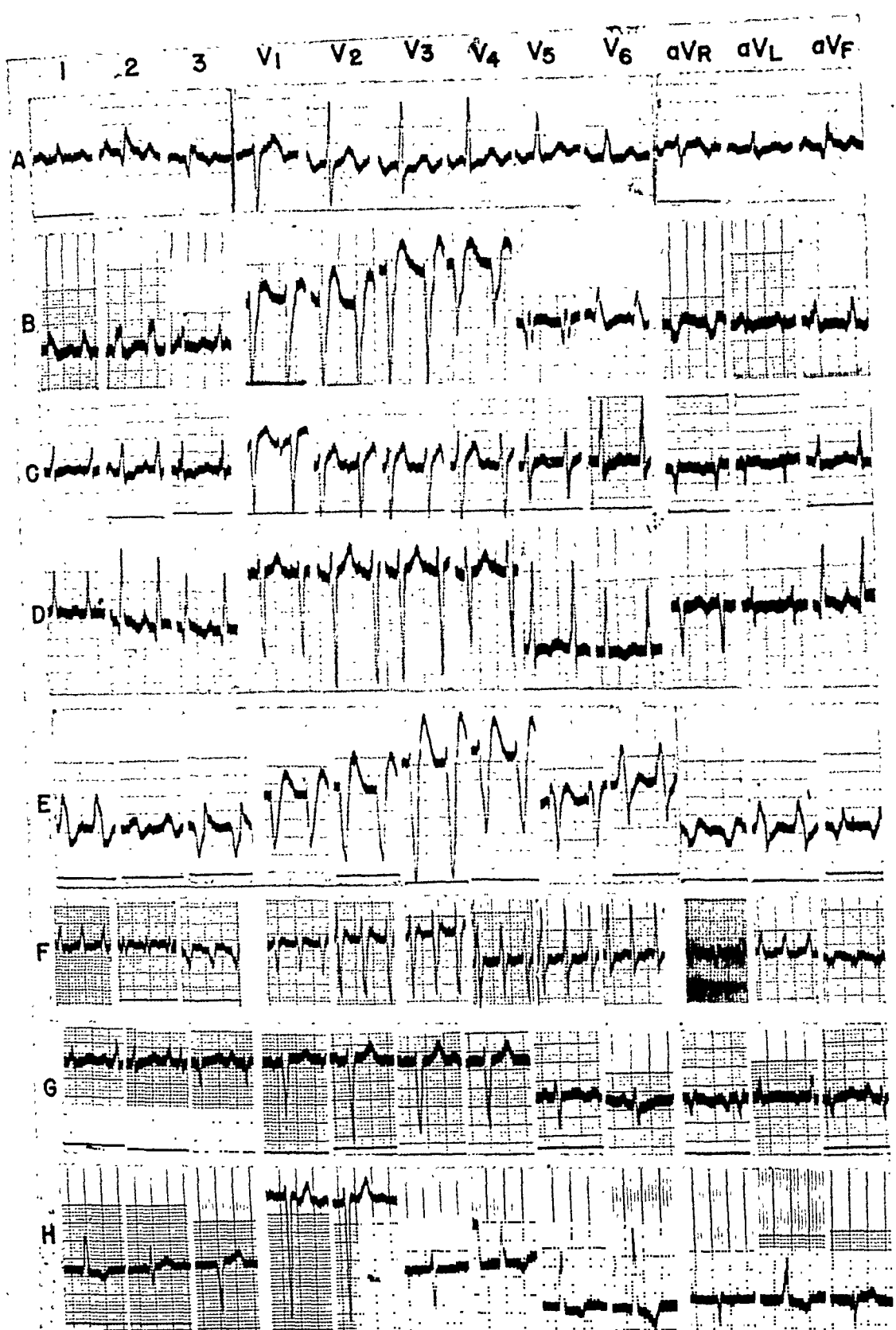


Fig. 10.—Electrocardiographic findings in old, healed posterior infarction. A, Case 95; B, Case 96; C, Case 97; D, Case 98; E, Case 99; F, Case 100; G, Case 101; and H, Case 102.

Electrocardiographic Findings.—An electrocardiogram obtained on the third hospital day, after the administration of 0.3 Gm. of digitalis, is reproduced in Fig. 6,E. Lead aV_F displayed a slurred Q wave, which consumed 0.03 to 0.04 second from onset to nadir and ranged from 30 to 50 per cent of the amplitude of the succeeding R wave. The QR complex in lead aV_F was therefore regarded as abnormal and representative of posterior infarction. The dome-shaped RS-T segment and inverted T wave were suggestive, but not pathognomonic, of a recent infarct in the process of organization. The findings in Lead aV_F carried over into Leads II and III, which were also indicative of posterior infarction. The RS-T segment depression in Lead aV_L and Lead I was regarded as a reciprocal manifestation of a recent infarct, rather than as a digitalis effect. The pattern in Lead V_6 was suggestive of an outlying zone of ischemia, but was also compatible with left ventricular hypertrophy. The initial R wave was within normal limits in Leads V_1 and V_2 , but showed a significant decrease in amplitude in Leads V_3 and V_4 . The question arose as to whether the decrease in the R wave of Leads V_3 and V_4 was a transitional zonal phenomenon or whether it was the result of an old, patchy anteroapical infarct. Since the R wave in the precordial leads should have been exaggerated in the presence of an uncomplicated posterior infarct, the decrease in Leads V_3 and V_4 was considered significant and most likely due to a patchy anteroapical infarct.

Pathologic Findings.—The heart weighed 598 grams and showed an old posterior infarct comparable in size and position to that in Case 93 (Fig. 9), with a recent extension into the posterolateral wall of the apex similar to that in the previous case. The infarct extended in patchy fashion through the subendocardial three-fourths of the posterior wall and adequately explained the abnormal QR pattern in Leads aV_F , III, and II. The recent lateral extension might have been a factor in the abnormal T waves in Leads V_6 and aV_L , but caused no abnormality in the initial phase of the QRS complex. An old, healed patchy infarct was found in the apical one-third of the anteroseptal wall and was presumably responsible for the abnormal reduction in the amplitude of the initial R wave in Leads V_3 and V_4 .

CASE 95.—A 67-year-old man was admitted to the hospital in coma with right hemiplegia due to cerebral hemorrhage. Past history was not obtainable. The patient did not regain consciousness and died on the ninth hospital day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the morning of admission is reproduced in Fig. 10,A. Lead aV_F displayed a slurred Q wave, which consumed 0.04 second from onset to nadir, followed by an R wave, which was coarsely notched on its descending limb. The QR pattern in Lead aV_F was diagnostic of posterior infarction and carried over into Leads II and III. The slight elevation of the RS-T junction and inversion of the T wave in these leads raised the question of a recent lesion in the process of organization, but could also have represented a fixed pattern associated with a healed posterior infarct. The transitional zone was displaced to the right. Precordial Leads V_2 through V_4 showed a minute Q wave and an abnormally tall, slurred R wave and depressed RS-T junction, attributable in part to left ventricular hypertrophy and in part to reciprocal effects from destruction of the posterior wall. The QRS interval was 0.13 second. Left bundle branch block was excluded by the initial downward deflection in precordial leads over the left ventricle, together with the absence of marked delay in the attainment of the peak of the R wave in Leads V_5 and V_6 . Since the intrinsicoid deflection was significantly later in Lead aV_F than in the precordial leads over the left ventricle, it was concluded that the main conduction defect was in the posterior wall of the left ventricle and was the result of the posterior infarct.

Pathologic Findings.—The heart weighed 701 grams and exhibited an aneurysmal protrusion of the posterobasal portion of the left ventricle, filled with a partially calcified laminated clot. The basal half of the posterior wall of the left ventricle was completely fibrosed and was reduced to a thickness of 2.0 to 3.0 millimeters. The aneurysm was a part of a huge healed infarct which involved almost the entire posterior and lateral walls of the left ventricle and extended into the left side of the posterior half of the septum, as illustrated in Fig. 11. Microscopic examination showed no evidence of recent activity. Thus, the RS-T segment changes in

Leads aV_F , II, and III were representative of a fixed pattern, which is commonly found in association with ventricular aneurysm.^{19,20} The deep, broad Q wave in Lead aV_F was a manifestation of the posterior infarct, and the succeeding R wave may have been derived from patches of preserved muscle in the subepicardial portion of the apical half of the posterior wall. In spite of the demonstration of the continuation of the infarct into the posterior portion of the septum, the conduction defect was placed in the posterior wall for reasons given in the discussion of the electrocardiogram. The extensive involvement of the lateral wall had not been recognized electrocardiographically, but was sufficiently patchy in the apical two segments to have been responsible for the small Q wave and broad, slurred R wave of Lead V_6 . Since the anterior wall was not infarcted, the tall R and T waves in Leads V_2 through V_4 were probably due in part to hypertrophy of the anterior wall and in part to reduction in the opposing potentials, normally created during activation of the posterior wall.



Fig. 11.—Roentgenogram of the injected heart in Case 95, showing aneurysm of posterior wall filled with a partially filled mural thrombus.

CASE 96.—A 58-year-old man had had transient retrosternal oppression and dyspnea on exertion for one year, but gave no definite history of a prolonged attack. Although he had been maintained on digitalis for the preceding six months, congestive failure developed, necessitating hospitalization. He remained in failure despite therapy and died on the eleventh hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 10, B. Four other tracings taken at intervals during hospitalization showed no change in rhythm or in the QRS-T contour. An auricular tachycardia was constantly present, the rate varying between 200 and 215 per minute. A complete A-V block was found in all

tracings. The ventricular rate ranged from 125 to 150 and the QRS interval measured 0.16 second. These findings could have been explained either by a ventricular tachycardia or by a nodal tachycardia complicated by an intraventricular conduction defect. The uniformity in the QRS-T pattern at varying ventricular rates in five tracings was against ventricular tachycardia, because of the tendency of an idioventricular pacemaker to shift in position. In an analysis of the tracing based on the supposition of a pacemaker in the A-V node, two possible explanations for the conduction defect were considered, namely, left bundle branch block and a lesion in the free wall of the left ventricle. Left bundle branch block was excluded by the combination of initial negativity of the left ventricular cavity, as indicated by the Q waves in Leads V_5 and V_6 , with initial positivity of the right ventricular cavity, indicated by the distinct, but brief, initial R wave consistently recorded in Lead aV_R . The beginning phase of the QRS complex was upright in the first three precordial leads and averaged 2.0 mm. in amplitude in Leads V_1 and V_2 and decreased to 1.0 mm. in Lead V_3 . In view of these findings, the broad, slurred QS deflection of Lead V_4 and the W-shaped QRS complex of Lead V_5 were considered diagnostic of a transmural infarct of the anterolateral wall of the left apex. The abnormally broad initial Q wave and subsequent slurred R wave of Lead V_6 were attributed to extension of the infarct subendocardially into the lateral wall. The marked RS-T segment displacement in the precordial leads was in part secondary to the conduction defect and in part the result of digitalization. The absence of significant change in serial tracings was strongly against a recent lesion. Lead aV_F revealed a distinctive pattern characterized by a slurred Q wave, which consumed 0.03 second from onset to nadir, followed by a coarsely notched ascending limb of the R wave, which required 0.08 second from onset to peak. Although the Q wave of Lead aV_F was only 1.5 mm. in depth and 15 per cent of the amplitude of the succeeding R wave, the QR complex was definitely abnormal because of the slurring, notching, and prolongation of both the Q wave and ascending limb of the R wave. This pattern was considered diagnostic of a conduction defect in the posterior wall of the left ventricle and was attributed to an old posterior infarct.

Pathologic Findings.—The heart weighed 516 grams and revealed an extensive old healed infarct which involved the entire circumference of the left ventricle in the two apical segments and the posterolateral wall in the three basal segments, as illustrated in Fig. 12. The infarct was transmural in the anteroapical region and in limited portions of the posterior wall. The lateral and most of the posterior portion of the infarct was characterized by dense fibrosis and scattered islands of preserved muscle in the subendocardial one-half to two-thirds of the wall and by patchy fibrosis with considerable preserved muscle in the subepicardial layer. The distribution of the lesion in the anterolateral and posterior walls satisfactorily explained the abnormal Q wave and the broad, slurred or notched, late R wave in Leads V_5 , V_6 , and aV_F . Although such a pattern might be recorded in these leads as a result of left bundle branch block complicated by massive septal infarction, this was very unlikely in the present case because of the limitation of the septal infarct to the apical third. Furthermore, the septal infarct did not extend high enough to account for the complete A-V block.

CASE 97.—A 52-year-old man gave a history of an attack of prolonged retrosternal oppression, followed by congestive failure, one year previously, leading to hospitalization elsewhere. He was maintained on digitalis ever since and was essentially asymptomatic until the fortnight prior to hospital admission, during which he had recurrent attacks of angina pectoris. He was admitted in congestive failure and responded satisfactorily until the fourteenth day, when he suddenly died of pulmonary embolism.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-four hours after admission is reproduced in Fig. 10, C. In Lead aV_F there was a small Q wave 0.02 second in duration, 1.0 mm. in depth, and approximately 15 per cent of the amplitude of the succeeding R wave. Judged solely by the foregoing characteristics, the Q wave of Lead aV_F could not be considered abnormal; however, the distinct notching of the succeeding upstroke and the delay in the intrinsicoid deflection indicated that the QR complex, taken as a whole, was abnormal. The QR pattern in Lead aV_F pointed strongly toward a conduction defect in the posterior wall of the type produced by infarction of its subendocardial portion. The depressed RS-T junction

and inverted T wave of Lead aV_F were probably in part secondary to the conduction defect and in part due to superimposed digitalis action. The transitional zone was displaced leftward to Position V_6 . In Lead V_6 there was a minute initial Q wave, 1.0 mm. in depth, followed by a slurred ascending limb of the R wave, 0.05 second in duration. This pattern was more in keeping with left ventricular hypertrophy than with extension of the posterior infarct into the lateral wall. Since the QRS complex in Lead aV_L was an almost exact reciprocal of that in Lead aV_F , it presumably represented cavity potentials transmitted through the mitral orifice to the left arm. The possibility of lateral infarction should have been further investigated by supplementary high precordial and axillary leads.

Pathologic Findings.—The heart weighed 553 grams and showed an old healed infarct of the subendocardial one-third of the posterolateral wall in the basilar three segments. This infarct was comparable in position to, though not quite as large as, the posterolateral infarct in the basi-



Fig. 12.—Roentgenogram of the injected heart in Case 96.

lar three segments in Case 96 (Fig. 12). The posterior portion of the infarct was well correlated with the abnormal QR pattern of Lead aV_F , and the lateral portion of the infarct may have contributed to the QRS pattern of Lead V_6 .

CASE 98.—A 45-year-old man was admitted to the hospital in coma, which was due to a cerebral hemorrhage of hypertensive origin. No past history was obtainable. No cardiac glycosides were given. Death occurred twenty-four hours later.

Electrocardiographic Findings.—An electrocardiogram obtained ten hours after admission is reproduced in Fig. 10, D. Lead aV_F displayed a Q wave, which ranged from 0.02 to 0.03 second

in duration, 2.0 to 3.0 mm. in depth, and 10 to 20 per cent of the amplitude of the succeeding R wave. Judged by the foregoing characteristics alone, this Q wave was not definitely abnormal; however, the fact that the Q wave was followed by a slurred upstroke, which consumed 0.05 second from onset to peak, indicated that the QR complex was abnormal. The QR pattern in Lead aV_F pointed to a conduction defect in the posterior wall secondary to infarction of the subendocardial layer. The slightly elevated RS-T junction and inverted T wave were suggestive of an organizing lesion, but might have represented a fixed pattern. The initial deflection was upright in all precordial leads and was abnormally tall and prolonged in Leads V_5 and V_6 . The slight delay in onset of the intrinsicoid deflection in Leads V_5 and V_6 , together with the inversion of the T wave, was referable to left ventricular hypertrophy. The small equiphasic RS complex of aV_L was attributed to transmission of potential variations of the transitional zone to the left arm, as the result of semivertical position of the heart. The findings in Leads II and III resembled those of Lead aV_F and were suggestive of a subendocardial posterior infarct.

Pathologic Findings.—The heart weighed 732 grams and exhibited a patchy fibrosis scattered through the subendocardial one-half of the entire posterolateral wall of the left ventricle. The patchy fibrosis was attributed to multiple small, healed infarcts of the type produced by circulatory collapse. The pattern in Lead aV_F was well correlated with the findings in the posterior wall at autopsy. The involvement of the lateral wall was not evident electrocardiographically, partly as the result of the semivertical position and partly, of the failure to take high precordial and axillary leads.

CASE 99.—A 64-year-old man had noted exertional dyspnea for one and one-half years and typical angina pectoris for eight months. He was hospitalized elsewhere two months previously because of a prolonged retrosternal pain and since then suffered from angina decubitus. He was admitted to the hospital in severe congestive heart failure and died three days later. Digitalis was given before and during hospitalization.

Electrocardiographic Findings.—An electrocardiogram obtained on the second day is reproduced in Fig. 10, E. The heart rate was 140 per minute; the P-R interval, 0.18 second; and the QRS interval, 0.16 second. Leads aV_F and III displayed a broad initial downstroke, requiring 0.05 second from onset to nadir, followed by an exceptionally broad, slurred upstroke, requiring 0.08 second from onset to peak. This was originally interpreted as evidence of a very large posterior infarct, causing great delay in conduction through the posterior wall. In view of the fact that Leads aV_L and V_6 showed a broad, slurred initial R wave, suggestive of left bundle branch block, an alternative interpretation should have been considered for Lead aV_F , namely, that it was a transitional lead and reflected the potential variations of the posterior part of the septum and the adjacent portions of the right and left ventricles. Under these circumstances, the initial broad Q wave would have been representative of recordings often obtained through semidirect leads over the epicardial surface of the right ventricle in cases of left bundle branch block, whereas the late R wave would have been the result of the delayed activation of the posterior basal surface of the left ventricle adjacent to the septum. If this explanation were correct, the findings in Leads aV_F and III could have been the result of left bundle branch block uncomplicated by infarction. Close inspection of Leads V_1 , V_2 , and V_3 revealed a minute initial downward deflection, followed by a small, momentary R wave and then a deep, broad S wave. These leads were evidently reflecting the potential variations of the epicardial surface of the right ventricle. The small Q wave was attributed to initial negativity of the right ventricular cavity, as a result of activation of the septum from right to left; the small R wave was presumably derived from activation of the free wall of the right ventricle; and the deep S wave was a left ventricular phenomenon. Leads V_5 and V_6 were probably transitional and a more typical pattern of left bundle branch block would have been expected if Lead V_7 or V_8 had been taken.

Pathologic Findings.—The heart weighed 803 grams, as the result of very marked left ventricular hypertrophy with secondary right ventricular dilatation and hypertrophy. A relatively small healed infarct was found localized to the apical third of the posterior wall of the left ventricle and the left side of the contiguous septum. The distribution of the infarct in the two apical segments was like that in the first segment in Case 100 (Fig. 13), except that the lesion

was limited to the subendocardial half of the free posterior wall. Infarction confined to the apical third of the septum could not have produced left bundle branch block. The prolongation of the QRS complex was undoubtedly due to a lesion high in the septum, which had been unrecognized because of failure to take multiple sections in the region of the bundle of His. Furthermore, the infarct localized to the subendocardial portion of the apical one-third of the posterior wall could scarcely have been responsible for the deep, broad Q wave in Lead aV_F. In view of the autopsy findings, the pattern in Lead aV_F was most likely a transitional zonal phenomenon, as the result of transmission of potential variations of the epicardial surface in the immediate vicinity of the posterior portion of the interventricular septum to the left leg. The initial Q wave was representative of negative potentials from the endocardial surface of the right side of the septum and cavity, which were transmitted through the posteroseptal portion of the right ventricular wall, and the late R wave was derived from the delayed activation of the posteroseptal wall of the left ventricle.

CASE 100.—A 63-year-old man gave a history of exertional dyspnea for two years and paroxysmal nocturnal dyspnea and ankle edema for two months. He denied chest pain. Despite the administration of digitalis by his family physician, he was in extreme congestive failure on hospital admission and died twenty-six hours later.

Electrocardiographic Findings.—An electrocardiogram obtained twelve hours before death is reproduced in Fig. 10, F. An auricular tachycardia of 225 per minute was present with a P-R interval of 0.20 second and 1:1 ventricular response. The QRS interval of 0.11 second, the initial upstroke in precordial leads over the left ventricle, and the delayed intrinsicoid deflection in Leads V₆ and aV_L were indicative of incomplete left bundle branch block. The question arose as to whether the W-shaped QS complex in Lead aV_F was due to posterior infarction or whether it was merely secondary to the incomplete left bundle branch block and due to transmission of the potential variations of the normal right ventricle and transitional zone to the left leg. The differential diagnosis was aided by the contour of the ventricular complex and by measurements of the time interval between its onset and the apex of each of its three phases. The measurements from the beginning of the QRS complex were: 0.02 second to nadir of initial downstroke; 0.05 second to peak of upstroke; 0.07 second to apex of the final downward deflection. If a heart with incomplete left bundle branch block were in horizontal position, the transmission of the potential variations of the epicardial surface of the normal right ventricle to the left leg might lead to the registration of a triphasic QRS in Lead aV_F, consisting of a small Q wave due to early negativity of the right ventricular cavity, a brief R wave derived from activation of the posterior wall of the right ventricle, and a deep S wave secondary to activation of the free wall of the left ventricle. However, this possibility was excluded in the present case by the fact that the peak of the upstroke occurred too late to have been derived from activation of a normal right ventricle. Furthermore, the findings were not attributable to a semihorizontally placed heart with incomplete left bundle branch block (analogous to the situation in Case 99), because the upstroke was too early to have been derived from activation of the posterobasal wall of the left ventricle and would not have been followed by a second downward deflection. On the other hand, the findings in Lead aV_F could be adequately explained either by incomplete transmural infarction of the posterior wall of the left ventricle in a heart in intermediate position or by infarction of the septum in a horizontally placed heart.¹⁷ Because of the early death of the patient, studies to establish the position of the heart and the site of the infarct were not made.

Pathologic Findings.—The heart weighed 577 grams and exhibited a healed incomplete transmural infarct of the posteroapical wall of the left ventricle which continued into the septum and for a short distance into the right ventricle, as outlined in Fig. 13. Although the infarcts in Cases 99 and 100 were comparable in position, that in the latter case was relatively more extensive, both in its distribution between endocardium and epicardium and in its surface area in reference to cardiac size. The findings in Lead aV_F could have been adequately explained by the posterior portion of the infarct, if the heart were in intermediate position, or by the septal portion, if the heart were in horizontal position. The latter alternative was favored

because of the rarity of marked Q-wave abnormalities in association with infarction limited to the posteroapical portion of the heart.

CASE 101.—A 48-year-old woman was admitted to the hospital in coma with left hemiplegia. Past history was unobtainable. Death occurred on the fourth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the second day, before the administration of cardiac glycosides, is reproduced in Fig. 10,G. The relatively small R and deep S waves in Leads V_1 through V_6 indicated that these leads reflected the potential variations of the right ventricle and the equiphasic RS complex in Lead V_6 was considered transitional. The apparent depression of the RS-T segment in Lead V_6 was an artifact, due to wandering of the string, secondary to poor application of the electrode. The prominent R wave in Lead aV_L



Fig. 13.—Roentgenogram of the injected heart in Case 100.

was of left ventricular origin and the associated inverted P wave suggested transmission from the posterobasal wall of the left ventricle. The notching of the R wave in Lead aV_L was abnormal and attributed to a posterobasal lesion. The findings in Lead aV_L coupled with those in the precordial leads indicated horizontal position with backward displacement of the apex. Both the cardiac position and the registration of a relatively early intrinsicoid deflection and prominent late S wave in Lead aV_F indicated that the potential variations of the left leg were transmitted principally from the right side of the septum and the posteroinferior wall of the right ventricle rather than from the corresponding portions of the left ventricle. The distinct Q wave which preceded the RS complex in Lead aV_F is an abnormal finding in right ventricular

leads and may occur as a result of left bundle branch block, right ventricular hypertrophy, or septal infarction.¹⁷ Since the first alternative was excluded by the QRS interval of 0.09 second and the second alternative, by the QRS pattern in right precordial leads, consideration was given to the possibility that this Q wave was a manifestation of infarction of the left side of the septum. A lesion in this position could have interfered with the spread of impulses through the left Purkinje plexus to responsive septal muscle and could thus have indirectly favored activation of septal remnants by impulses distributed through the right Purkinje system. This would have caused initial negativity of the endocardial surface of the right side of the septum and should have produced a Q wave in leads facing this side of the septum. The Q wave in right ventricular Lead aV_F was adequately explained by the presence of infarction of the left side of the septum, but the absence of the expected Q waves in leads from the right side of the precordium failed to confirm the diagnosis. Infarction, if present, was presumably healed because of lack of T-wave abnormalities.

Pathologic Findings.—The heart weighed 639 grams and displayed a healed infarct of the apical third of the posterior wall of the left ventricle, which continued into the left side of the posterior half of the septum and crossed slightly into the right ventricle. The position of this infarct was similar to that in Case 100 (Fig. 13), except that it was limited to the subendocardial one-half to three-fourths of the posterior wall of the left ventricle and failed to reach the junction with the lateral wall. The relatively early R wave and late S wave in Lead aV_F could not be correlated with the distribution of the lesion in the posteroapical wall of the left ventricle. If the potential variations of this portion of the heart had had the dominant effect on the recordings in Lead aV_F, an abnormal Q wave and late R wave would have been expected. The Q wave in Lead aV_F was not derived primarily from the extension of the infarct into the posterior wall of the right ventricle, since activation of the septum in the usual manner should have produced early positivity of the right ventricular cavity and, hence, an initial upstroke in right ventricular leads, irrespective of the presence or absence of infarction of the outer wall. The presence of an abnormal Q wave in Lead aV_F could be correlated with infarction of the left side of the posterior half of the septum and its absence from right precordial leads could be accounted for by the preservation of the anterior half of the septum.

CASE 102.—A 57-year-old man in 1944 gave a history of protracted retrosternal pain radiating down the left arm. He was hospitalized on several occasions during the next three years because of recurrent congestive failure. Physical examination showed evidence of syphilitic aortic insufficiency. Death occurred in February, 1947, from congestive failure.

Electrocardiographic Findings.—An electrocardiogram reproduced in Fig. 10, H was obtained in May, 1945, while the patient was taking digitalis in doses of 0.1 Gm. daily. Auricular fibrillation was consistently present in a series of tracings over a period of two and one-half years and the QRS pattern in the precordial and limb leads showed no significant changes. The findings in the precordial leads were typical of left ventricular hypertrophy. The resemblance of Lead aV_L to Leads V₅ and V₆ indicated that the potential variations of the lateral wall of the left ventricle were transmitted to the left arm. Lead aV_F of all tracings displayed a triphasic QRS complex, consisting of small, brief Q and R deflections and a relatively deep S wave. The last two phases of the pattern in Lead aV_F coupled with the findings in Lead aV_L suggested a horizontal position of the heart with predominant transmission of the potential variations of the right side of the septum and epicardial surface of the posteroinferior wall of the right ventricle to the left leg. The Q wave in Lead aV_F was abnormal and, like that in Case 101, was believed referable to infarction of the left side of the septum. The initial R wave in Leads V₁ and V₂, which faced the anterior wall of the right ventricle, was also comparable to the findings in Case 101 and, by analogy, suggested that the anterior portion of the septum had been spared.

Pathologic Findings.—The heart weighed 755 grams and exhibited a healed infarct of the apical half of the posterior wall of the left ventricle which continued into the posterior half of the septum and crossed slightly into the right ventricle. The distribution of this infarct in the three apical segments was comparable to that in the second segment in Case 100 (Fig. 13), except that this lesion failed to reach the junction of the posterior wall with the lateral wall of the

left ventricle. The small Q, small R, and deep S wave in Lead aV_F could be correlated with the infarct of the posterior part of the septum, but not with the lesions of the free posterior wall of the left or right ventricle, for the same reasons as in Case 101.

CASE 103.—A 69-year-old man entered the hospital because of right-sided pleural pain, fever, and a productive cough of one week's duration. Physical and roentgen examination established the diagnosis of pneumonia. Hospital course was uneventful until the twelfth day, when the patient suddenly died. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram, including esophageal leads obtained on the eighth day, was published as Fig. 1 of a previous report.¹¹ A presumptive diagnosis of posterior infarction had been made from the presence of a QR_2 and QS_3 in an earlier electrocardiogram, taken on the second hospital day, but the age of the lesion was indeterminate from the T-wave pattern in that tracing. This led to the repetition of the electrocardiogram, including Lead aV_F and esophageal leads. The diagnosis of recent incomplete transmural posterior infarction was established by the abnormal QS complex and typical displacement of the RS-T segment in Lead aV_F of the tracing on the eighth hospital day and was confirmed by the deep Q deflection, minute R wave, elevated RS-T junction, and coved negative T wave in esophageal leads at the ventricular level. The tall, upright T waves in the first four precordial leads were considered reciprocal to the posterior infarct and the dome-like inversion of the T wave in Lead V_6 , in view of the absence of a Q wave, was attributed to an outlying zone of ischemia in the lateral wall.

Pathologic Findings.—The heart weighed 584 grams and exhibited a large transmural infarct of approximately two weeks' duration involving practically the entire posterior wall. The infarct was comparable in position to that in Case 92 (Fig. 8), except that it reached the posterior aspect of the apex. Thus, the prediction based on the pattern in Lead aV_F and the esophageal leads conformed closely with the infarct found at autopsy. Death was due to rupture of the infarct with hemopericardium. Since the esophageal leads were obtained four days before death, it is probable that this procedure played no part in the terminal rupture.

CASE 104.—A 65-year-old man was in good health until the day of admission to the hospital, after he was seized with severe retrosternal pain while watching a ball game. He was brought to the hospital in profound circulatory collapse and died thirty-two hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram was obtained three hours after the onset of the present illness, but is not reproduced because of the close resemblance of the limb leads to those in Case 88 (Fig. 3). Auricular fibrillation was present, complicated by complete A-V block with a regular ventricular rhythm of 44 per minute. The form of the QRS complex indicated a nodal pacemaker. The marked elevation of the RS-T segment in Leads aV_F , II, and III was typical of a recent posterior infarction. The minute Q and relatively tall R waves in these leads, together with the straightened RS-T segments and tall, upright T waves, were compatible with a very early lesion. The first phase of the QRS complex was upright in all precordial leads except for Leads V_{3R} and V_1 , which revealed an initial downstroke and a late notch on the succeeding ascending limb. Marked depression of the RS-T segment was found in Leads V_2 through V_5 and also in Lead aV_L , whose QRS complex resembled that of Lead V_4 . The displacement of the RS-T segment in Leads V_2 through V_5 was considered reciprocal to that in Lead aV_F . A diagnosis was made of recent posterior infarction, which extended into the septum to produce the complete A-V block and possibly the findings in Leads V_1 and V_{3R} .

Pathologic Findings.—The heart weighed 340 grams and exhibited a large, recent transmural infarct involving the entire posterior wall and posterior half of the septum. The distribution in all segments was comparable to that in the three basilar segments in Case 87 (Fig. 2), except for the absence of septal perforation. From the microscopic findings, it was believed that the transmural lesion of the posterior wall and septum antedated the electrocardiogram. The minute Q wave and relatively tall R wave in Lead aV_F indicated that the interval of three hours between the onset of symptoms and recording of the electrocardiogram was too short for ob-

literation of the response of the posterior wall to the activating impulse, but not for interruption of conduction through the A-V node. The latter could be correlated with the transmural lesion of the posterior half of the base of the septum. Since the anterior wall was intact, the depression of the RS-T segment in Leads V_2 through V_6 was reciprocal to the posterior infarct, whereas the QS pattern in Leads V_1 and V_{3R} may have been a manifestation of the septal lesion.

CASE 105.—A 74-year-old man was admitted to the hospital for the resection of carcinoma of the sigmoid. He had had hypertension for four years, but gave no definite history of myocardial infarction. He had no cardiac symptoms during the next eighteen months' observation, prior to death from metastases. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained preoperatively is reproduced in Fig. 14, A. Leads V_5 , V_6 , and aV_L displayed a minute Q wave and slightly delayed intrinsicoid deflection, attributable to left ventricular hypertrophy. A similar QR deflection was present in Lead I and a small R and R' wave were found in Lead III, separated by a deep S wave. The standard leads thus showed definite left axis deviation, but were not diagnostic of infarction. On the other hand, Lead aV_F displayed a deep Q, 0.035 second in duration from

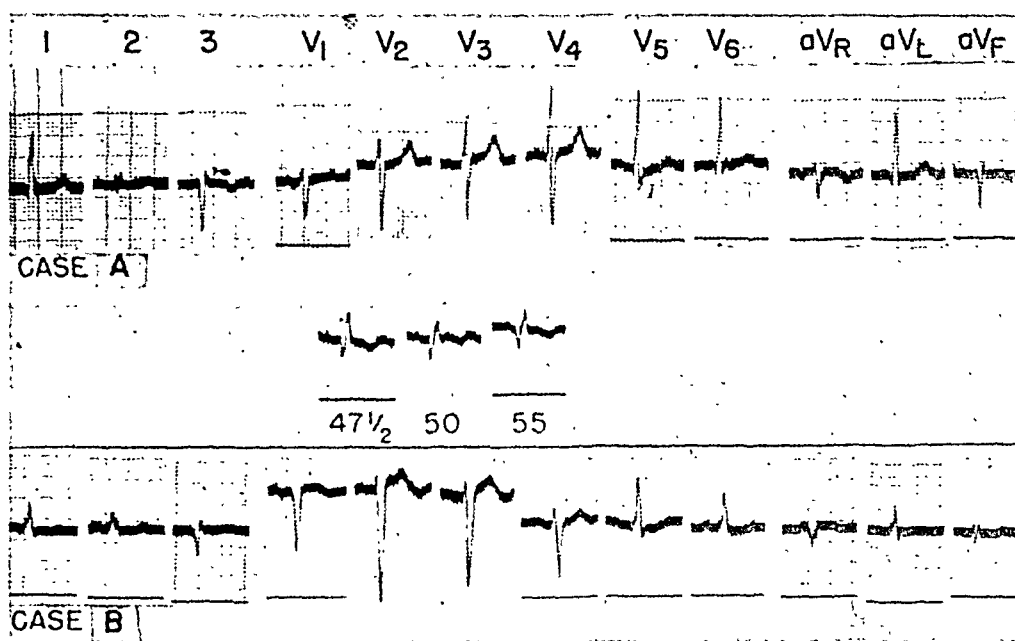


Fig. 14.—Electrocardiographic findings in (A) posterior infarction (Case 105) contrasted with those in (B) semihorizontal position with left ventricular hypertrophy, but without infarction.

onset to nadir, followed by a small R wave. The findings in Lead aV_F were interpreted as evidence of posterior infarction. The initial R wave, which was found in Lead III, but not in Lead aV_F , was derived from the initial negativity of the left arm. This was registered as a Q wave in Lead aV_L and as an R wave in Lead III. For further evidence, esophageal leads were obtained and confirmed the diagnosis made from Lead aV_F . The abnormally deep Q wave and slurred, prolonged ascending limb of the R wave recorded at E_{50} and E_{55} were diagnostic of posterior infarction. Although the inverted T wave in esophageal leads raised the question of organizing infarct, it proved on subsequent study to represent a fixed residue. Tracings repeated periodically during the next eighteen months showed no significant change and thus confirmed the diagnosis of old posterior infarction.

Pathologic Findings.—The heart weighed 410 grams and revealed a well-localized transmural infarct of the posterior wall of the second, third, and fourth segments, as outlined in Fig. 15. Thus, the autopsy findings confirmed the conclusions from Lead aV_F and from esophageal leads.

The electrocardiogram in Case B (Fig. 14), is included for purposes of contrast. The patient was a 60-year-old woman, who had been taking digitalis irregularly and was admitted in congestive failure. The delay in onset of the intrinsicoid deflection in Leads V_5 , V_6 , and aV_L was interpreted as evidence of left ventricular hypertrophy. The findings in these leads were thus comparable to those in Case 105. The delayed peak of the R wave in Lead I and the small, notched complex in Lead II likewise resembled those of the corresponding leads in Case 105. Lead III in Case B (Fig. 14) showed a QR complex, which raised the question of posterior infarction. The unipolar extremity leads were also of considerable aid in the analysis of the standard leads and in the establishment of a diagnosis in this case. Because of the RSR' com-



Fig. 15.—Roentgenogram of the injected heart in Case 105.

plex in Lead aV_F , the suspicion of posterior infarct was dismissed. The deep Q wave of Lead III was derived from the potential variations of the left arm and was roughly the reciprocal of the record in Lead aV_L , as would be expected from the fact that the connections to the left arm in Lead III are the reverse of those in Lead aV_L . The heart weighed 460 grams and exhibited left ventricular hypertrophy. No evidence of posterior infarction was found at autopsy, thereby supporting the diagnosis made with the aid of Lead aV_F .

These two cases merely illustrate the fact that Lead aV_F is preferable to Leads II and III for the interpretation of lesions of the posterior wall. The limitations of Lead aV_F , as well as those of the standard leads, will be illustrated in subsequent cases.

CASE 106.—A 78-year-old man had had exertional dyspnea and angina pectoris for two years and was admitted to the hospital in severe congestive failure complicated by bronchopneumonia. Death occurred two days later.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day, after the administration of 1.6 mg. of Cedilanid followed by 0.3 Gm. of digitalis, is reproduced in Fig. 16, A. The precordial leads, which were not included in the illustration, merely showed evidence of left ventricular hypertrophy and digitalis effect. There was an underlying sinus rhythm with frequent auricular premature beats, which were coupled in Lead aV_R and formed short runs of auricular tachycardia in other leads. The standard leads showed left axis deviation with an upright initial deflection in Leads I and II and a deep Q wave in Lead III. The question arose as to the significance of Q_3 . The initial deflection in Lead aV_F was down-

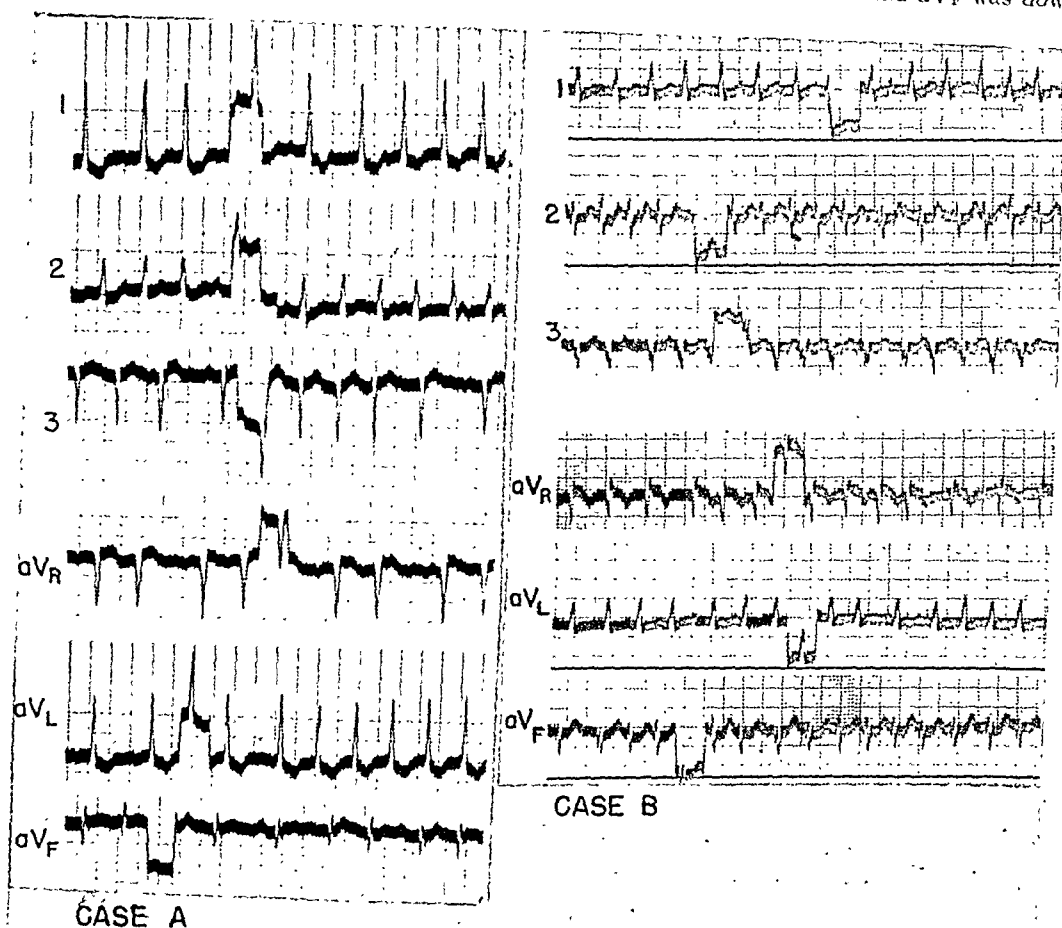


Fig. 16.—Respiratory fluctuations in QRS pattern in Leads aV_F and III of (A) posterior infarction (Case 106), and (B) left ventricular hypertrophy without infarction.

ward in all but three cycles, where there was a questionable minute preliminary R wave. The Q wave of Lead aV_F measured 0.02 second from onset to nadir and ranged from 2.0 to 5.0 mm. in depth, or from 66 to 200 per cent of the amplitude of the succeeding R wave. The changing Q/R ratio was attributed to respiratory shifting in cardiac position. Since the Q/R ratio was consistently within the abnormal zone, the findings in Lead aV_F were considered strongly suggestive of an old, healed subendocardial posterior infarction; however, they could not be considered as pathognomonic, because of the relatively low voltage of the QR complex, the short duration of the Q wave and the questionable preliminary R deflection in three cycles.

Pathologic Findings.—The heart weighed 595 grams and exhibited an old, healed patchy infarct of the subendocardial one-half of the posterobasal portion of the left ventricle, as illustrated in Fig. 17. This infarct was apparently responsible for the QR pattern in Lead aV_F. In view of the fact that the basal portion of the posterior wall was involved and the apical portion spared, a respiratory shift, which periodically favored transmission of the potential variations of a more distal portion of the posterior wall to the left leg, could have accounted for the intermittent initial R wave.

Case B of Fig. 16 is included for contrast purposes. The patient in this case was a 65-year-old man who had been admitted to the hospital in coma with hemiplegia. The electrocardiogram showed auricular fibrillation with rapid ventricular rate. Left axis deviation was present. Lead II showed an RS complex preceded by a distinct Q wave in approximately one-third of the cycles, and Lead III showed a notched QS deflection. Thus, the standard leads

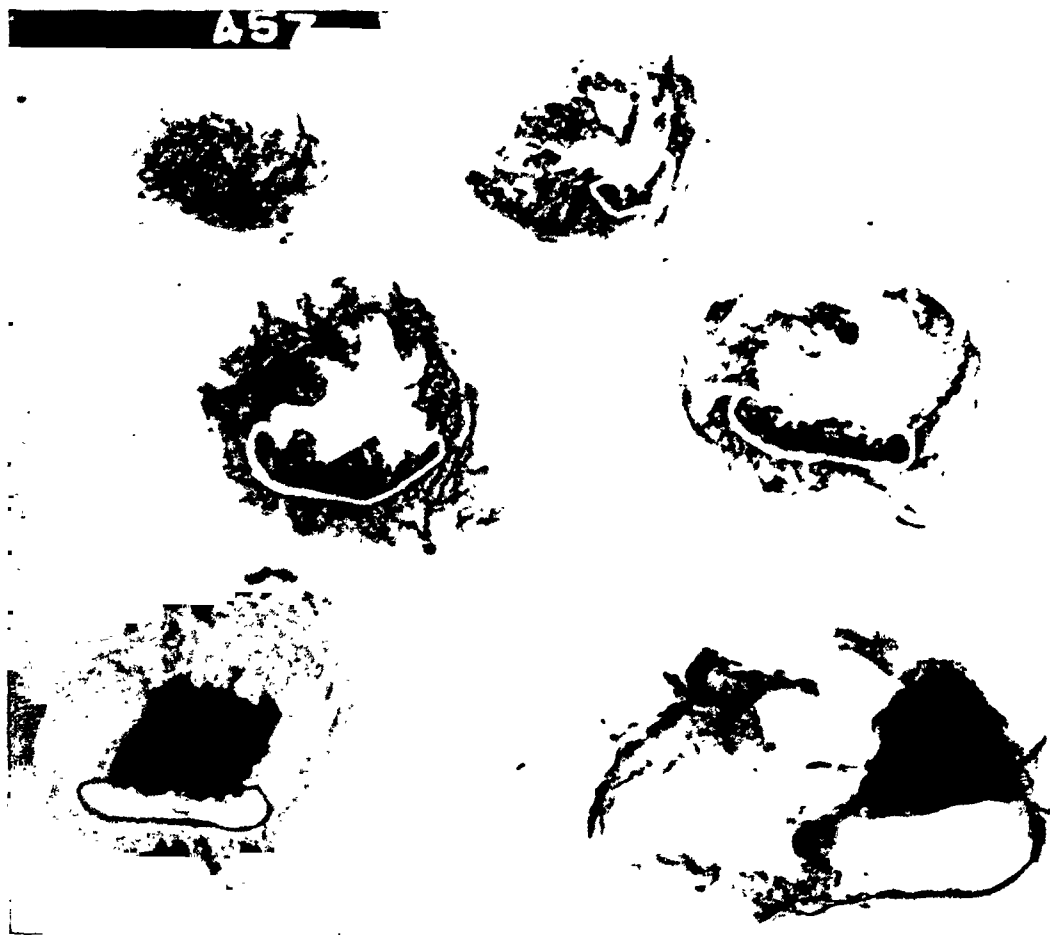


Fig. 17.—Roentgenogram of the injected heart in Case 106.

were strongly suggestive of posterior infarction. The QRS pattern in Lead aV_F was also quite variable. An initial Q wave, ranging up to 0.02 second in duration, was detectable in about one-half of the cycles. This Q wave was followed by an upstroke, which sometimes reached and sometimes crossed the isoelectric line, and then by a relatively deep S wave, which constituted the major deflection. If such a pattern had been present in all the cycles of Lead aV_F, it would have justified a diagnosis of septal infarction in a transverse heart. However, the remaining cycles showed an initial R wave, which approached the amplitude of the succeeding S wave. The intermittent presence of an R wave of these proportions was against both septal and posterior infarction. The variable QRS pattern in Lead aV_F in this case was best explained by semihorizontal position of the heart with transmission of potential variations of the posterior

part of the interventricular septum to the left leg. The respiratory shifting in the points of contact between the heart and diaphragm was considered responsible for the variability in the QRS complex. The patient died of cerebral hemorrhage. The heart weighed 700 grams and exhibited left ventricular hypertrophy, but showed no evidence of infarction.

These two cases thus illustrate the precautions which must be taken in the interpretation of Lead aV_F when respiratory or postural variations in the contour of the QRS complex are present.

Electrocardiograms *A*, *B*, and *C* of Fig. 18 are included to illustrate the difficulties which arise in the interpretation of Leads aV_F , II, and III. In Lead aV_F of Fig. 18, *A* there was a 1.0 mm. Q wave and a 4.0 mm. R wave, making a Q/R ratio of 25 per cent. The time interval of 0.02 second from onset to nadir of the Q wave in Lead aV_F was within normal limits, whereas the duration of the upstroke of the R wave was also normal. A somewhat broader, slurred Q wave was present in Lead III and constituted 50 per cent of the amplitude of R_3 and 33 per cent of the tallest R wave in the standard leads. There was an 0.5 mm. Q wave in Lead II, which was about 10 per cent of the associated R wave. The Q/R ratio was thus abnormal in Lead III, borderline in Lead aV_F , and within normal limits in Lead II. Because of the low voltage in Lead aV_F and the normal duration of both the Q and R wave, one is not justified in attaching pathologic significance to the borderline ratio in this lead. The patient whose electrocardiogram was reproduced in Fig. 18, *A* died of cirrhosis and had a normal heart at autopsy.

Attention is next directed to the QR complex in Leads II and III of Fig. 18, *B*. Q_2 was 1.5 mm. in depth and approximately 20 per cent of the succeeding R wave. Q_3 was 5.0 mm. deep and was nearly 50 per cent of the largest R wave in the standard leads. Thus, the QR pattern in Leads II and III and the associated inversion of T_3 were strongly suggestive of posterior infarction. The close correspondence of the QRS complex in Lead aV_L with that in Lead V_6 indicated transmission of the potential variations of the lateral wall of the left ventricle to the left arm, whereas the upright deflection in Lead aV_F was believed to have been derived from the posterior wall of the left ventricle. The low voltage was probably due to loss in transmission between the diaphragm and leg and the slurring was of the type commonly associated with low voltage. The findings in Lead aV_F were strongly against posterior infarction. Because of the very low voltage of the potentials referred to the left leg during ventricular activation, the recordings in Leads II and III were practically the reciprocal of those in Leads aV_R and aV_L , respectively. Thus, Q_2 was a manifestation of the initial positivity of the right arm, whereas Q_3 was the result of initial positivity of the left arm. The inverted T_3 was the reciprocal of the upright T wave in Lead aV_L . When they were analyzed in the light of the findings in the unipolar extremity leads, it was evident that the Q wave in Lead II and the Q and T waves in Lead III were not due to posterior infarction. The depression of the RS-T segment in left ventricular leads was attributable to a dose of 1.6 mg. of Cedilanid, which had been given before the electrocardiogram was taken. The patient whose electrocardiogram is reproduced in Fig. 18, *B* died in cardiac failure. Autopsy revealed a heart weighing 520 grams with left ventricular hypertrophy due to hypertension, but showed no evidence of posterior infarction.

The electrocardiogram in Fig. 18, *C* was obtained on a 62-year-old hypertensive man who had been admitted to the hospital in shock following a sudden severe retrosternal pain which radiated down both arms and straight through to the back. He had received no cardiac glycosides. In Lead aV_F there was a Q wave 3.0 to 4.0 mm. deep and approximately 75 per cent of the succeeding R wave. The time interval from onset to nadir of the Q wave in Lead aV_F was 0.03 second and that from the beginning to peak of the R wave was 0.04 second. A 2.0 mm. Q wave was found in Lead II, which was two-thirds of the succeeding R wave. Q_3 was 5.0 to 6.0 mm. in depth and was equal to the tallest R wave of the standard leads. On the basis of these findings, the QR complex in Leads aV_F , II, and III was considered abnormal and an electrocardiographic diagnosis of posterior infarction was made. A tall upright T wave with a concave upward RS-T segment, but without significant displacement of the RS-T junction, was registered in Leads aV_F , II, and III. Such a pattern was more in keeping with acute pericarditis than with recent infarction, but did not exclude the latter. Death occurred sixteen hours after the onset of the pain and one-half hour after the electrocardiogram was obtained. Autopsy

disclosed a dissecting aneurysm which had ruptured into the pericardium, causing distention of the sac with 400 c.c. of slightly clotted blood. There was no evidence of myocardial infarction either by gross or microscopic examination. The hemopericardium adequately accounted for the RS-T contour in Leads aV_F , II, and III. A Q-wave pattern, resembling that of posterior infarction, has been reported previously in association with hemopericardium due to dissecting aneurysm.²¹ It has been suggested that the signs suggesting posterior infarction may be the result of ischemia of the posterior wall from compression of the right coronary artery.²² In experimental coronary occlusion of animals, abnormal Q waves make their appearance before histologic signs of infarction are detectable. It is possible that sufficient interference with coronary flow to the posterior wall had been produced in this case to alter its response to the activating impulse and thereby result in the registration of an abnormal QR complex. This might have occurred long enough before death to result in the registration of an abnormal QR complex in an electrocardiogram taken one-half hour ante mortem, yet might have been present too short a time for the development of the histologic signs of myocardial infarction.

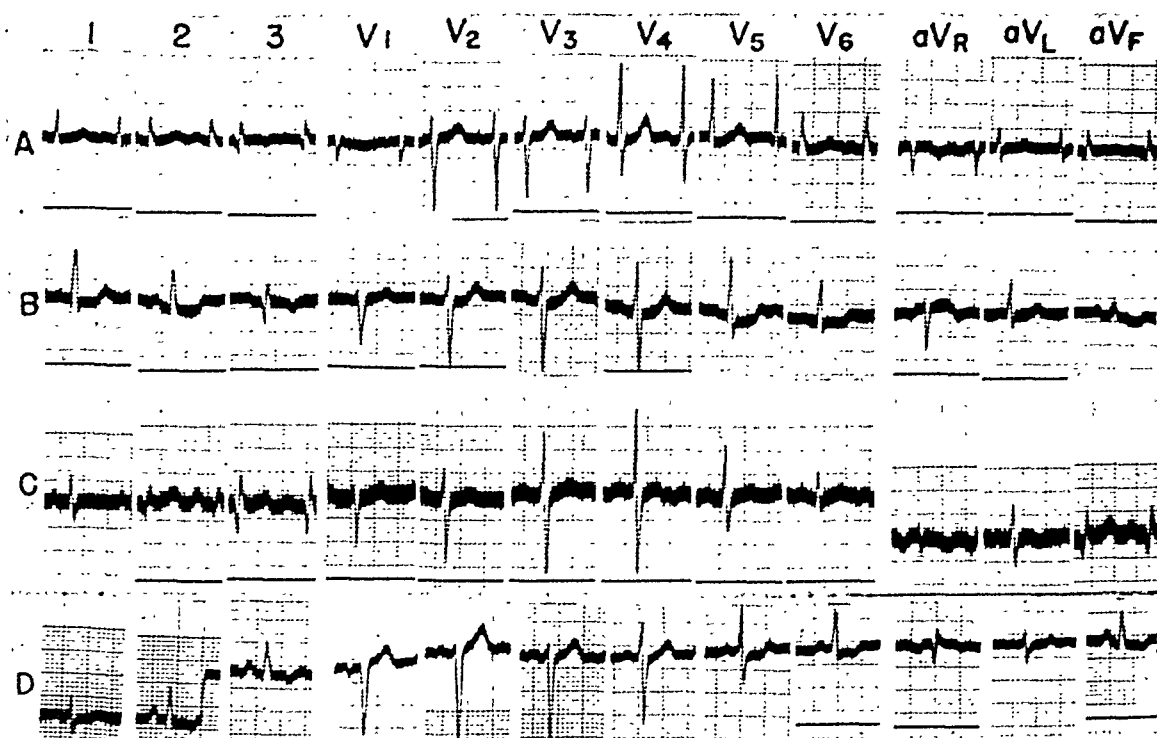


Fig. 18.—Shortcomings of Lead aV_F and the standard leads. A, Normal heart; B, left ventricular hypertrophy without infarction; C, hemopericardium due to dissecting aneurysm; and D, recent postero-basal infarction (Case 107).

CASE 107.—A 56-year-old man had suffered from bronchial asthma since 1937 and was first admitted to the hospital in August, 1941, because of lobar pneumonia. His blood pressure was normal and his heart was negative to physical and roentgen examination. He re-entered in March, 1943, because of typical angina pectoris and exertional dyspnea during the preceding four months. Examination revealed moderate hypertension, left ventricular enlargement, and failure. Digitalis was instituted and maintained for the rest of his life. Following discharge, he was fairly comfortable until May, 1944, when he again began to have frequent attacks of angina pectoris. He was readmitted on June 6, 1944, after twenty hours of continuous retrosternal oppression and dyspnea. He became symptom free soon after hospitalization and remained so until the thirteenth day, when severe retrosternal pain recurred and resulted in death one-half hour later.

Electrocardiographic Findings.—An electrocardiogram obtained on June 7, 1944, forty-two hours after the onset of the pain which led to his final admission, is reproduced in Fig. 18,D. The QRS pattern in the precordial leads was not remarkable, and the displacement of the RS-T segment in Leads V_1 and V_2 was attributed to digitalis. There was a tendency to right axis deviation, as a result of the semivertical position of the heart. In Lead aV_F there was a minute, slurred Q wave, which was considered normal because of a 0.22 second duration and an amplitude only 10 per cent of that of the succeeding R wave. These findings were carried over into Leads II and III, and the QR complexes in these leads were also within normal limits. The slight depression of the RS-T junction and inversion of the T wave in Leads aV_F , II, and III were not attributable to a myocardial lesion, since patterns of this type may be observed in these leads as a normal variant or as a result of digitalis action. This tracing was therefore interpreted as showing a semivertically placed heart and moderate digitalis effect, but no evidence of myocardial infarction. This opinion was strengthened by a comparison of this electrocardiogram with former tracings in 1941 and 1943. The former electrocardiograms included only Leads I, II, III, and chest Leads V_2 , V_4 , and V_6 . No significant difference was found in the QRS pattern in any of these leads and only minor differences were found in the RS-T segments and T waves, which were attributable to differences in degree of digitalis effect. Furthermore, a repeat tracing taken on the ninth hospital day and including the three standard and six precordial leads showed almost identical QRS complexes to those of corresponding leads in Fig. 16,D. The RS-T segments and T waves in the precordial leads had not changed significantly; however, the RS-T segments in Leads II and III were slightly more depressed, whereas the T waves had become low upright. This T-wave evolution was atypical of myocardial infarction, but unfortunately was not investigated further by esophageal leads.

Pathologic Findings.—The heart weighed 458 grams and showed an organizing infarct confined to the subendocardial portion of the basilar half of the posteroseptal wall of the left ventricle, as outlined in Fig. 19. By microscopic examination, this infarct was estimated to be about two weeks in age and was limited to the subendocardial one-fourth to one-half of the wall. The lack of an abnormal QRS pattern in Lead aV_F and the absence of significant change in the QRS complex of Leads II and III after the development of the infarct was probably due to localization to the subendocardial portion of the basilar half of the posterior wall. The T-wave changes, even in retrospect, were not diagnostic of posterior infarction, but along with the clinical history should have aroused sufficient suspicion to have led to the taking of esophageal leads. This case illustrates the limitations of both Lead aV_F and Leads II and III in the diagnosis of posterior infarction.

CASES 108 TO 123, INCLUSIVE.—The salient electrocardiographic and pathologic findings in these cases have been summarized in Table I, in order to conserve space.

COMMENT

Interpretation of Lead aV_F .—

Relation of QRS Pattern in Lead aV_F to Cardiac Position: Because of the galvanometric connections employed,^{23,24} the recordings in Lead aV_F represent chiefly, though not quite exclusively, the potential variations of the left leg. The direction of potential change in the left leg at the arrival of the impulse in the ventricles depends primarily upon the surface of the septum that faces downward, whereas the potential variations of the left leg throughout the remainder of ventricular activation and repolarization are governed principally by those of the epicardial surface that rests upon the diaphragm.

The portion of the septum that faces toward the left leg and the surface of the heart in juxtaposition with the diaphragm are subject to variation, not only in different persons, but also in a given individual, depending upon posture

and respiration.^{25,26} The electrical position of the heart is classifiable into five categories, namely, vertical, semivertical, intermediate, semihorizontal, and horizontal.²⁵ The portion of the heart that faces downward and has the predominant influence on the potential variations of the left leg consists of: (1) the left side of the septum and posterior wall of the left ventricle when the heart is in vertical, semivertical, or intermediate position; (2) the right side of the septum and the posterior wall of the right ventricle in horizontally placed hearts; and (3) the posterior end of the septum and adjoining walls of the right and left ventricles in semihorizontal position.



Fig. 19.—Roentgenogram of the injected heart in Case 107.

Determination of cardiac position constitutes the first step in the interpretation of the findings in Lead aV_F . This is accomplished through a study of the QRS pattern in the unipolar limb leads in reference to that in the precordial or other semidirect leads, as discussed in detail in a previous communication.²⁶ Vertical and semivertical position can generally be established from the presence of one of the following patterns in Lead aV_L : a relatively small R and deep S wave, and an equiphasic RS complex or multiphasic QRS of low voltage. On the other hand, when Lead aV_L displays a prominent R wave with or without a small Q deflection and/or S wave, the heart may be in horizontal, semihorizontal, or intermediate position. Further differentiation depends upon the

findings in Lead aV_F and is usually easy when the voltage of the QRS complex exceeds 0.5 millivolt. Intermediate position of the heart is established by the demonstration of one of the following patterns in Lead aV_F : a monophasic upright deflection; an RS complex consisting of a prominent R wave, 5.0 mm. or more in height, followed by a relatively small S wave; or a QR complex of 0.5 millivolt or greater. Horizontal position is established by the presence of relatively small R and deep S waves in Lead aV_F , but may be manifested by a QS complex, as a normal variant, analogous to that found in Lead V_1 . The latter must be differentiated from the abnormal QS complex, found in Lead aV_F as a manifestation of septal infarction, when the heart is in horizontal position, and from that occurring as a result of complete transmural posterior infarction when the heart is in intermediate to vertical position. Semihorizontal position is indicated by the presence of a diphasic or multiphasic QRS complex of low voltage in Lead aV_F , generally beginning with an upstroke, occasionally with a Q wave. The latter finding must be distinguished from the abnormal QR complex of posterior infarction.

Derivation of the Normal QR Complex in Esophageal Leads and in aV_F : A QR complex constitutes the usual finding in leads obtained from the lower esophagus and from other parts of the body that face toward the left side of the septum and posterior wall of the left ventricle. During the brief interval between the start of the spread of the impulse through the septum and its arrival at the posterior wall of the left ventricle, negative potentials derived from septal activation are transmitted from its left endocardial surface through the left ventricular cavity and resting myocardium to the epicardium of the posterior wall, and are registered as a Q wave through contiguous esophageal leads. As soon as the impulse reaches and begins to activate the subendocardial layer of the posterior wall, the polarity of its epicardial surface suddenly reverses, and the Q wave is replaced by the upstroke of the R wave. Because of the later arrival of the impulse at the basal than at the apical portion of the posterior wall, the Q wave in esophageal leads opposite the former is normally longer in duration and larger in amplitude than the Q wave in leads opposite the latter.

When the heart is in vertical, semivertical, or intermediate position, the initial negative potentials transmitted through the posterior wall of the left ventricle are directed downward as well as backward and may normally reach the left leg in sufficient magnitude to be recorded as an initial downstroke in Lead aV_F . In semihorizontally placed hearts, the low voltage QRS complex may begin with a small Q wave for the same reason. The normal Q wave in Lead aV_F is subject to variation in duration and amplitude, depending upon whether it is transmitted principally from the posteroapical or posterobasal aspect of the left ventricle. The time from onset to nadir of the normal Q wave generally ranges from 0.01 to 0.02 second, but may reach 0.03 second in leads facing the posterobasal wall of the left ventricle. The amplitude of the normal Q wave is almost invariably less than 25 per cent of that of the succeeding R wave, except in the presence of low voltage of the entire QRS complex, when greater ratios may be encountered.

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN CASES 108 TO 123, INCLUSIVE

CASE NO.	QRS DUR. (SEC.)	Q IN aV _F			COMMENTS ON FINDINGS IN LEAD aV _F	PATHOLOGIC FINDINGS.
		DUR. (SEC.)	AMP. (MM.)	% R aV _F		
108	0.09	0.03	2.0	50	Abnormal QR due to posterior infarct	Old, patchy transmural infarct of entire post. wall and posterior one-third of septum; similar to Fig. 8
109	0.12	—	—	—	Not diagnostic due to LBBB and semihorizontal position	Old, patchy transmural infarct distributed throughout post. wall in a manner comparable to lesion in second segm. of Fig. 15
110	0.14	0.04	0.5	10	Right bundle branch block; abnormal broad Q due to posterior infarct	Old patchy infarct of subendocardial one-half of entire posterior septal wall and posterior one-third of left side of septum; similar to Fig. 5
111	0.09	0.05	5.0	Infinity	Abnormal QS due to septal portion of infarct	Old transmural infarct distributed through apical two-thirds of posterior wall and posterior one-third of septum in a manner comparable to lesion in fourth segm. of Fig. 8
112	0.09	0.05	4.5	900	Abnormal QR due to posterior infarct	Old transmural infarct of apical one-half of post. wall comparable to lesion in fourth segm. of Fig. 15
113	0.11	—	—	—	Not diagnostic due to incomplete LBBB despite intermediate position	As in Case 112
114	0.12	—	—	—	Not diagnostic due to LBBB and horizontal position	Old transmural infarct of apical one-third of post. wall of L.V. ext. into posterior one-half of septum and apical one-third of post. wall of R.V.; similar to second segm. of Fig. 13

115	0.14	—	—	—	Not diagnostic due to LBBB and horizontal position	Old transmural infarct of apical one-third of post. wall; similar to lesion in second segm. of Fig. 15
116	0.09	—	—	—	Not diagnostic despite intermediate position	Old transmural infarct limited to apical one-fifth of post. wall, comparable to lesion in second segm. of Fig. 15
117	0.09	0.03	2.5	100	Abnormal QR due to posterior infarct	Old infarct of subendocardial two-thirds of middle third of post. wall, comparable in position to lesion in third and fourth segm. of Fig. 15
118	0.08	0.03	2.5	100	Abnormal QR due to post. inf.	As in Case 117
119	0.08	0.02	1.0	30	Borderline QR due to post. inf.	As in Case 117
120	0.10	0.01	0.5	12	Not diagnostic despite semi-vertical position	As in Case 117
121	0.08	0.02	2.5	40	QR complex with notched upstroke diagnostic of infarction	Old transmural infarct of basal two-thirds of post. wall ext. into posterior one-half of basal third of septum similar to lesion in third to sixth segm. of Fig. 8
122	0.09	0.03	3.0	30	Abnormal QR due to posterior infarct	Old infarct of subendocardial one-third of basal third of post. wall, comparable to lesion in Fig. 19
123	0.08	—	—	—	Not diagnostic despite vertical position	Old infarct of subendocardial one-third of basal third of post. wall, comparable to lesion in Fig. 19
Segm.—segment. Ext.—extending.					LBBB—Left bundle branch block. Post. Inf.—Posterior infarct.	Post. wall when unqualified refers to free posterior wall of left ventricle.

Derivation of the Abnormal QS and QR Patterns in Esophageal Leads: The QRS pattern in semidirect precordial leads is well correlated with the distribution of the infarct through the subjacent anterolateral wall,²⁰ and that in semidirect esophageal leads corresponds closely with the distribution of the lesion through the contiguous posterior wall of the left ventricle. Thus, an abnormal QR complex represents the characteristic finding in esophageal leads opposite an infarct of the subendocardial layer of the posterior wall, and an abnormal QS deflection is the typical finding in esophageal leads subtending a complete transmural posterior infarct. When the subendocardial layer is infarcted, the onset of activation of living muscle in the more superficial layer is delayed until the impulse has traversed or circumvented the infarct. During this period, negative cavity potentials, derived from activation of the septum and intact portions of the free wall of the left ventricle, are transmitted through the infarcted posterior wall to be recorded as an abnormally deep and prolonged Q wave in contiguous esophageal leads. If the entire thickness of the wall has been destroyed, the string returns to the isoelectric line to complete a QS deflection, but if the impulse meets responsive muscle in the more superficial layers, the Q wave is followed by an R wave. The amplitude of the R wave is reduced in rough proportion to the residual intact muscle. Thus, the Q/R ratio is abnormally increased, not only by the exaggeration of the Q wave, but also by the reduction of the R wave. When the posterior infarct is patchy in distribution, neighboring esophageal leads may display a normal Q wave, followed by a notched or coarsely slurred, prolonged upstroke, presumably reflecting a circuitous pathway of the impulse between islands of preserved myocardium.

Derivation of the Abnormal QR Complex in Lead aV_F: When the heart is in vertical, semivertical, or intermediate position, the potential variations of all or part of the epicardial surface of the posterior wall of the left ventricle are transmitted downward, as well as backward, to have the predominant effect upon the pattern in Lead aV_F. Differences between the QRS pattern in esophageal leads and that in aV_F in this range of cardiac positions are chiefly referable to the larger area of epicardium subtended by the electrode on the left leg. Thus, a large posterior infarct that is partly transmural, as evidenced by a QS deflection in some esophageal leads, will usually be manifested by a QR complex in Lead aV_F, because of the fact that the area responsible for the pattern in Lead aV_F is generally large enough to include part of the marginal or ischemic zones of the infarct. If a QS deflection is recorded in Lead aV_F as a manifestation of infarction of the free posterior wall, it is almost invariably a transient finding observed during acute stage and is replaced by a QR complex as the lesion heals. The distinction between this type of QS deflection and the more common QS pattern occurring in Lead aV_F of horizontally placed hearts will be considered. A small posterior infarct, detectable through esophageal leads, may or may not be manifested by diagnostic signs in Lead aV_F, depending upon whether the potential variations of the left leg are derived chiefly from the involved or from the intact portion of the posterior wall.

Criteria for the Differentiation Between the Normal and Abnormal QR Complex in Lead aV_F: The individual variations in the duration of the normal Q wave in Lead aV_F and in the ratio of its amplitude to that of the succeeding normal R wave have been discussed. The QR complex associated with posterior infarction is subject to much wider range, depending upon the relation of the epicardial surface of the infarct to the diaphragm and the relative thickness of the infarcted and uninfarcted portions of the myocardium. Although no sharp dividing line can be drawn between the normal QR complex in Lead aV_F and that associated with posterior infarction, the following criteria seem to offer the best separation and are employed in this study: QR complexes of 0.5 millivolt or more are considered diagnostic of posterior infarction when the Q wave measures 0.03 second or more from onset to nadir and exceeds 25 per cent of the amplitude of the associated R wave, and are classed as borderline to strongly suggestive when they meet one of these two requirements. QR deflections of low voltage that conform with both of the foregoing criteria are regarded as strongly suggestive of posterior infarction, but when the Q-wave duration is 0.04 second or more, they are classed as definitely abnormal. When a QR complex classifiable as borderline to strongly suggestive of posterior infarction is found in a patient with previous electrocardiographic evidence of a normal pattern in Lead aV_F, the serial change is considered diagnostic of posterior infarction. The pattern in Lead aV_F of tracings taken within twenty-four hours of the onset of pain is considered diagnostic of posterior infarction when a QR complex is accompanied by classical displacement of the RS-T segment, even though the duration and/or amplitude of the Q wave are within normal limits. QR complexes of 0.5 millivolt or more in Lead aV_F, characterized by a distinct Q wave followed by a prolonged, notched, or coarsely slurred upstroke are considered abnormal, even though the duration of the Q wave and/or Q/R ratio do not meet the foregoing minimal requirements. The Q wave reflects initial negativity of the left ventricular cavity and thus indicates that the conduction defect responsible for the prolongation and notching of the ascending limb of the R wave is located in the free wall of the left ventricle rather than in the septum. This type of QR pattern is associated with healed patchy posterior infarction and constitutes an expression of alteration in the course of the activating impulse due to the interspersing of dense patches of fibrosis and islands of intact myocardium. A comparable QR pattern might be expected as a manifestation of dense fibrosis due to other etiological factors, such as inflammation, but these are relatively rare in comparison with myocardial infarction. A broad, notched R wave of 0.5 millivolt or more in Lead aV_F, without an antecedent Q wave, is probably representative of a conduction defect in the posterior wall rather than in the septum when measurements of the QRS interval are normal in the precordial leads and distinctly longer in Lead aV_F, but less than 0.12 second in all leads. Such a finding is considered suggestive of patchy posterior infarction. The foregoing criteria are not applicable in the presence of left bundle branch block, since Lead aV_F may display a broad, notched R wave when the heart is in vertical to intermediate position, an abnormal QR complex when in semihorizontal position,

and a broad QS pattern when in horizontal position, irrespective of the presence or absence of infarction.

Differentiation of the Normal and Abnormal QS Deflections in Lead aV_F: When the heart is in horizontal to semihorizontal position, the potential variations of the right side of the septum and epicardial surface of the right ventricle have the predominant effect upon the pattern in Lead aV_F and are registered in most normal subjects as an RS complex, consisting of a relatively small R wave derived mainly from activation of the septum, followed by a prominent S wave, representing negative potentials transmitted from the left ventricular cavity through the septum and right ventricle as these structures become depolarized. A QS complex may be recorded as a normal variant in place of the usual RS complex in Lead aV_F, probably as the result of loss of the small positive potentials in the course of transmission from the epicardial surface of the right ventricle to the left leg and perhaps in part, of a position facilitating transmission of opposing left ventricular cavity potentials through the mitral orifice into the left and right atria and thence to the left leg. A QS complex may also be recorded in Lead aV_F of horizontally placed hearts as a manifestation of septal infarction and is probably analogous in origin to the abnormal QS complex in Lead V₁ and in other precordial leads to the right of the transitional zone. The abnormal QS complex in leads facing the right side of the infarcted septum probably reflects an initial negativity of its endocardial surface, because of either a complete transseptal lesion that serves as a window capable of transmitting negative potentials from the left to the right ventricular cavity, or a lesion confined to the left side of the septum that results in the activation of intact septal remnants by way of the right rather than the left Purkinje plexus.¹⁷ This abnormal QS deflection tends to occur in Lead V₁ as a manifestation of infarction of the anterior half of the septum and in Lead aV_F of horizontally placed hearts as a manifestation of infarction of the posterior half of the septum.¹⁷ The QS deflection due to acute septal infarction may usually be recognized as abnormal from the presence of a characteristic pattern of the RS-T segment. The QS deflection due to healed septal infarction and that which occurs as a normal variant in Lead aV_F may usually be differentiated by the nature of the change induced by repetition of the tracing in the erect posture and during deep respiration. The replacement of the QS by an RS deflection as the heart shifts in position suggests that the QS deflection was a normal variant. On the other hand, the appearance of a triphasic QRS complex consisting of a small Q, small R, and deep S wave, or the appearance of an abnormal QR complex conforming to the criteria given, is indicative of infarction.

The problem of differentiating the abnormal QS complex due to septal infarction in a horizontally placed heart from that due to transmural infarction of the free posterior wall in an intermediate to vertically placed heart remains for consideration. The distinction is perhaps of more theoretic than practical interest, since large transmural infarcts of the posterior wall almost always extend into the septum, whereas infarcts of the posterior part of the septum continue into the free posterior wall. When the findings in Lead aV_L indicate vertical or semivertical position of the heart, a QS pattern in Lead aV_F is at-

tributable to transmural posterior infarction. When a tracing in a different posture reveals a triphasic QRS complex of normal duration in Lead aV_F consisting of a small Q, small R, and prominent S wave, the findings are referable to septal infarction. The deep S wave indicates predominant transmission of the potential variations of the left leg from the epicardial surface of the posterior wall of the right rather than the left ventricle, and the Q wave preceding the R wave indicates initial negativity of the right ventricular cavity due to septal infarction.¹⁷

Correlation of Electrocardiographic and Pathologic Findings.—

Esophageal leads were obtained in Case 103 during the acute stage and in Cases 86, 105, 129, and 152 after healing of the posterior infarct. All leads at the ventricular level in Case 103 revealed a deep prolonged Q wave followed by a small terminal R wave, despite the presence of a transmural infarct that ruptured four days after the studies were made. The pattern of the RS-T segment was in keeping with the organizing lesion found at autopsy. Leads at the ventricular level in Cases 86, 105, and 129 revealed a QR complex that was considered abnormal from both the standpoint of duration of the Q wave and Q/R ratio. These findings could be correlated with the distribution of the posterior infarct at autopsy. The Q/R ratio in leads from the ventricular level of Case 152 was within normal limits, but the coarse notching of the upstroke of the R wave pointed to a patchy infarct of the posterior wall. The lesion involved the subendocardial half of the entire posterior wall and was more extensive than had been anticipated from the esophageal leads.

Lead aV_F : The correlation between the findings in Lead aV_F and those at autopsy has been covered in each individual report, and remains to be summarized for the entire group of 110 cases. The pattern in Lead aV_F in each case has been classified, in accordance with the criteria already given, into one of the following three categories: diagnostic of infarction; borderline to strongly suggestive; and negative for infarction. The cases have been subdivided into six groups, in accordance with the size and position of the infarct in reference to the long axis of the posterior wall of the left ventricle: (a) infarction extending more than two-thirds of the length of the posterior wall; (b) involvement of the basal one-half to two-thirds; (c) infarction of the apical one-half to two-thirds; (d) infarction of the apical one-third; (e) involvement of the basal one-third; and (f) infarction of the middle one-third.

(a) *Findings in Lead aV_F in the Presence of Infarction Involving More Than Two-thirds of the Long Axis of the Posterior Wall:* Sixteen cases were observed with a recent infarct extending more than two-thirds of the length of the posterior wall, and twenty cases were observed with a healed lesion of comparable distribution. The findings in Lead aV_F were considered diagnostic of posterior infarction in twelve of the patients with a recent lesion and in eleven of those with a healed lesion and were regarded as diagnostic of septal infarction in two other patients with a healed lesion of the septum and posterior wall. A tracing obtained twenty-three hours after the onset of the pain in one other patient revealed displacement of the RS-T segment typical of recent posterior infarction, but failed to show an abnormal Q wave, probably because of an

interval of insufficient duration for obliteration of the response of the acutely infarcted posterior wall to the activating impulse. The electrocardiographic findings were classed as borderline to strongly suggestive in two other patients with recent infarction and in four of those with a healed lesion. Lead aV_F was negative in one case of recent infarction and in three cases of remote infarction. The diagnostic failure was attributable to horizontal position of the heart in three patients (Cases 35, 109, and 152), but occurred in one patient with extensive posterolateral infarction (Case 158) despite intermediate position of the heart. It is probable that the intact septal half of the posterior wall of the left ventricle was responsible for the normal R wave recorded in Lead aV_F in this case.

(b) *Findings in Lead aV_F in the Presence of Infarction of the Basal One-Half to Two-Thirds of the Posterior Wall:* A recent lesion of this distribution was found in three cases and a healed infarct in eight cases. The findings in Lead aV_F were considered diagnostic of posterior infarction in two of the former and three of the latter and were classed as borderline in two other cases of healed posterior infarction. A broad QS complex registered in Lead aV_F in another case was ascribed to left bundle branch block in a horizontal heart and was believed independent of the posterior and septal infarcts found at autopsy. Diagnostic failures were encountered in two cases of healed infarction due to horizontal position and in one case of recent infarction of the subendocardial one-fourth to one-half of the posterobasal wall (Case 107). This lesion was triangular in shape with its base near the atrioventricular groove and its apex in the middle portion of the posterior wall. A single record of Lead aV_F and serial tracings of the standard leads were not diagnostic of posterior infarction, despite semivertical position of the heart. In view of the normal QR complex in Lead aV_F in this case, it is probable that the potential variations of the left leg were transmitted mainly from the intact apical half of the posterior wall of the left ventricle.

(c) *Findings in Lead aV_F in the Presence of Infarction of the Apical One-Half to Two-Thirds of the Posterior Wall:* Six patients were observed with a recent infarct and fourteen with a healed lesion of this distribution. Lead aV_F provided definite evidence of posterior infarction in four patients from each group. Diagnostic signs were also present in three other patients with a healed infarct, but were ascribed to the lesion of the septum rather than to that of the posterior wall. The pattern in Lead aV_F was classed as borderline to strongly suggestive in one other patient with recent and three with healed infarction. Lead aV_F was negative in one patient with recent infarction (Case 81) and in four with a healed lesion (Cases 45, 73, 113, and 151). The diagnostic failures were attributable to horizontal position in three of the patients. The heart was in intermediate position in the other two (Cases 81 and 113) and the presence of an initial R wave instead of a Q wave in Lead aV_F was due to left bundle branch block.

(d) *Findings in Lead aV_F in the Presence of Infarction of the Apical One-Third of the Posterior Wall:* Of the thirty-three cases classified into this group, the lesion was recent in sixteen and healed in seventeen. The involvement of

the apical third of the posterior wall was primary in five cases and represented an extension from a primary anterior or lateral infarct in the remainder. Diagnostic signs in Lead aV_r referable to the lesion of the posterior wall were found in only one case of recent and two of healed infarction, whereas diagnostic findings referable to a septal extension were present in one additional case of recent and in two of healed infarction. Borderline signs were found in two cases of acute and one of old infarction. A very broad, slurred QR complex was present in Case 99, but was believed referable to an independent left bundle branch block in a semihorizontally placed heart rather than to the infarct of the apical third of the posteroapical wall. A QS complex 3.0 mm. deep, recorded in Lead aV_r in Case 137, could not be correlated with the subendocardial posterolateral infarct found at autopsy. Since the septum was intact, the QS complex was believed to represent a normal variant due to semihorizontal position. Lead aV_r was negative in the remaining twelve cases of recent infarction and ten cases of healed infarction. Horizontal position of the heart was primarily responsible for the diagnostic failures in eight of the former and in six of the latter. However, it is noteworthy that the heart was in vertical, semivertical, or intermediate position in the other four cases from each group with negative findings in Lead aV_r. In the four cases with a recent lesion (Cases 26, 37, 42, and 142) an extensive anterolateral infarct may have contributed to the diagnostic failure by reducing the negative left ventricular cavity potentials available for transmission through the posterior infarct to the left leg. The failure to detect evidence of the posterior infarct in Lead aV_r of the four patients with a healed lesion (Cases 18, 83, 116, and 157) and perhaps in the four patients with a recent lesion, as well, was probably due to predominant transmission of the potential variations of the left leg from portions of the posterior wall proximal to the apical third. This premise was supported by the lower incidence of diagnostic failures when the posteroapical infarct continued into the middle third of the posterior wall. Thus, diagnostic failures were encountered in eight of the fourteen patients with an infarct of the apical third of the posterior wall in an intermediate to vertically placed heart and in only two of the fourteen patients with an infarct of the apical one-half to two-thirds of the posterior wall in a comparably placed heart. Furthermore, the lack of diagnostic evidence in these two cases could be accounted for by the presence of left bundle branch block.

(c) *Findings in Lead aV_r in the Presence of Infarction of the Basal One-Third of the Posterior Wall:* One patient was observed with a recent infarct and three with a healed lesion confined to the basal third of the posterior wall. The QS complex recorded in Lead aV_r in the patient with the recent infarction was probably referable to the lesion of the septum rather than to the involvement of the posterior wall. Diagnostic failures were encountered in the other three (Cases 15, 75, and 123), despite semivertical to vertical position of the heart. The failure to detect evidence of the posterior infarct could be ascribed to involvement of the subepicardial layer in Case 15, but was probably due to predominant transmission of the potential variations of the left leg from portions of the posterior wall distal to the basal third in the other two patients.

This premise was supported by occurrence of only one diagnostic failure among eight patients with a posterobasal infarct that continued into the middle third of the posterior wall in an intermediate to vertically placed heart.

(f) *Findings in Lead aV_F in the Presence of Infarction of the Middle Third of the Posterior Wall:* A recent infarct of this distribution was found in one case and a healed infarct in five cases. The QS complex recorded in Lead aV_F in Case 135 could not be correlated with the recent subendocardial posterolateral infarct found at autopsy. Since the septum was not infarcted, the QS complex was believed to represent a normal variant due to horizontal position. The findings in Lead aV_F were considered diagnostic of posterior infarction in three of the five patients with a healed lesion and were classed as borderline in one additional patient. A normal QR complex was found in Lead aV_F of the remaining patient (Case 120), despite semivertical position. The lack of prolongation of the Q deflection and the low Q/R ratio were probably due to the small size of the infarct. The fact that a diagnostic failure occurred in only one of five patients with a relatively small infarct in the middle third of the posterior wall supports the premise that this portion of the posterior wall has the predominant effect on the potential variations of the left leg when the heart is in intermediate to vertical position.

Precordial leads face toward the endocardial surface of infarcts of the free posterior wall of the left ventricle, and thus would be expected to show changes opposite to those in leads facing the epicardial surface, such as the esophageal leads, and, in addition, Lead aV_F, when the heart is in intermediate to vertical position. Electrocardiographic studies were obtained during the acute stage of posterior infarction in fourteen cases, where autopsy subsequently confirmed the presence of the posterior lesion and excluded infarction of the anterior wall. In nine of the fourteen cases, precordial leads revealed reciprocal changes in the RS-T complex, characterized by acute depression of the RS-T segment during the stage of injury, followed by return of the RS-T junction to the isoelectric line accompanied by exaggeration in the amplitude of the erect T wave. These changes were found in Leads V₃ and V₄ in all nine cases, and extended to the right to Lead V₁ in four and to the left as far as position V₆ in four. Unusually tall R waves were also present in Leads V₁ through V₄ in four of the cases. The findings in the precordial leads of this group of fourteen patients contrasted sharply with those in a group of thirty patients with recent posterior infarction, complicated by acute or healed anterior infarction.²⁷ The precordial leads of the latter group showed no changes that could be ascribed to the reciprocal effects of the recent posterior infarct.

Standard Leads II and III failed to provide diagnostic evidence of posterior infarction in patients with normal Lead aV_F, because of the similarity in the galvanometric connections to the left leg. Furthermore, the application of the Pardee criteria or their various modifications to the interpretation of the findings in the standard leads led to errors in a number of cases where correct diagnoses could be made from the findings in Lead aV_F. The reason for this could be traced to the much greater influence of the potential variations of the upper extremities on the patterns in Leads II and III than upon that in Lead aV_F.

Occasional cases of posterior infarction, such as Cases 64, 105, and 125, were recognizable from the abnormal Q wave in Lead aV_F , but would have been missed from the standard leads because of the presence of a normal initial R wave in Lead III. This discrepancy was due to an initial negativity of the left arm, which was manifested by a Q wave in Lead aV_L , but by a reciprocal R wave in Lead III because of the reversal in galvanometric connections to the left arm. On the other hand, a deep Q_3 and inverted T_3 may be recorded in the absence of posterior infarction, as emphasized in a previous communication.¹¹ This is prone to occur: (a) in semihorizontal cardiac position when a tall initial R wave is recorded in Lead aV_L because of transmission of the potential variations of the anterolateral wall of the left ventricle to the left arm and an RS or RSR' complex of low voltage is recorded in Lead aV_F because of the transmission of the potential variations of the transitional zone to the left leg, as illustrated by Fig. 14,B; (b) in intermediate position when extracardiac conditions favor transmission of the potential variations of the left ventricle to the left arm, but interfere with their transmission to the left leg, as evidenced by a tall initial R wave in Lead aV_L and a minute, monophasic upright deflection in Lead aV_F and exemplified by Fig. 18,B. The Pardee Q_3 in both cases was recognized as a normal variant rather than a manifestation of posterior infarction by the fact that Lead aV_F displayed an RSR' complex in the former and a small monophasic R wave in the latter. Since the potential variations of the leg were small in comparison to those of the left arm in both cases, the recordings in Lead III represented chiefly the potential variations of the left arm and were the reciprocal of those in Lead aV_L because of the reversal in galvanometric connections. It is also noteworthy that the tracing reproduced in Fig. 18,B not only exhibited a Q_3T_3 pattern, but also a QR complex in Lead II compatible with posterior infarction, yet the heart merely showed uncomplicated left ventricular hypertrophy at autopsy. Reference to the Goldberger augmented leads showed that Q_2 was due to initial positivity of the right arm and that the QR complex in Lead II was the approximate reciprocal of the RS complex in Lead aV_R . Because of the demonstrated inferiority of the evidence furnished by the standard leads to that furnished by Lead aV_F for the diagnosis of posterior infarction, a statistical summary of the findings in the standard leads in this series of 110 cases does not justify the space required.

SUMMARY

The findings in Lead aV_F have been analyzed and correlated with cardiac position and with the pathologic findings in 110 patients with infarction of the posterior wall of the left ventricle. The infarct was recent in forty-three cases and healed in the other sixty-seven.

Determination of the electrical position of the heart was essential to the interpretation of the findings in Lead aV_F , since the direction of the initial phase of the QRS complex was dependent upon the surface of the septum that faced downward, whereas the potential variations of the left leg throughout the remainder of the cycle were governed principally by those of the epicardial surface that rested upon the diaphragm.

Findings in Lead aV_F in Thirty-Five Cases of Posterior Infarction With Electrocardiographic Evidence of Horizontal to Semihorizontal position of the Heart.—In twenty-two of the group, Lead aV_F displayed a small R and deep S wave, representative of the customary findings due to transmission of the potential variations of the right side of the septum and epicardial surface of the posterior wall of the right ventricle to the left leg and in no way suggestive of the posterior infarct found at autopsy. In nine others, a continuation of the infarct into the septum was manifested by one of the following three diagnostic patterns in Lead aV_F: a small Q, small R, and deep S wave; a small Q and tall late R wave similar to the pattern in Lead V₁ and referable to septal infarction with right bundle branch block; and a QS complex attributable to septal infarction after establishment of the presence of transverse position and exclusion of the QS complex that occurs as a normal variant under these circumstances. The latter was present in two of the thirty-five cases. Lead aV_F in the two remaining cases displayed a broad, slurred QS and QR complex, regarded as a manifestation of left bundle branch block in a horizontal and semihorizontal heart, respectively, and considered independent of the posterior and septal infarcts found at autopsy.

Criteria for the Diagnosis of Posterior Infarction in the Presence of Intermediate, Semivertical, or Vertical Position of the Heart.—Under these conditions, the potential variations of the epicardial surface of the posterior wall of the left ventricle had the predominant effect upon the QRS-T pattern in Lead aV_F. The abnormal QR pattern due to posterior infarction was differentiated from the normal QR complex in Lead aV_F by the time interval from onset to nadir of the Q wave, the ratio of the amplitude of the Q to that of the R wave, and the duration and contour of the ascending limb of the R wave. QR complexes of 0.5 millivolt or more, with a Q wave measuring 0.03 second or more from onset to nadir and a Q/R ratio over 25 per cent were considered diagnostic of posterior infarction. QR complexes that met part, but not all, of the foregoing requirements were generally classed as borderline to strongly suggestive, but were also considered diagnostic, provided that (a) the time interval from onset to nadir of the Q wave was 0.04 second or more; (b) the Q wave was followed by an abnormally prolonged, notched, or coarsely slurred upstroke; (c) the tracing was obtained within twenty-four hours of the onset of symptoms and showed classical displacement of the RS-T segment; or (d) previous tracings were available, showing perfectly normal patterns prior to the development of the borderline QR complex. QS deflections of 0.5 millivolt or more, which consumed 0.03 second or more from onset to nadir, were considered diagnostic of extensive transmural posterior infarction, provided it could be established that the heart was in intermediate to vertical position and not in horizontal or semihorizontal position.

Findings in Lead aV_F in Seventy-Five Cases of Posterior Infarction With Electrocardiographic Evidence of Intermediate to Vertical Position of the Heart.—On the basis of the criteria described, the findings in Lead aV_F were classed as diagnostic of posterior infarction in forty-two cases, borderline to strongly suggestive in seventeen cases, and negative in sixteen cases. The findings in

Lead aV_F , as classified into the foregoing three categories, were correlated with the size and position of the infarct in reference to the long axis of the left ventricle. Of thirty-one patients with infarction extending two-thirds or more of the length of the posterior wall, Lead aV_F was negative in only one. The normal QRS pattern in this case was probably due to the fact that the lesion was posterolateral in position and spared the septal half of the posterior wall. The incidence of diagnostic failures in patients with smaller posterior infarcts varied with the size and location of the lesion and was lowest when the infarct involved the middle third of the posterior wall, as shown by the following observations. Lead aV_F was negative in only one of five patients with infarction confined to the middle third of the posterior wall. On the other hand, the findings in Lead aV_F were negative in eight of fourteen patients with infarction confined to the apical third, but in only two of fourteen other patients in whom the posteroapical infarct continued into the middle third. Both of these failures were explained by the presence of left bundle branch block. The findings in Lead aV_F were negative in all three patients with infarction confined to the basal third of the posterior wall, but in only one of eight patients in whom the posterobasal lesion continued into the middle third. The latter failure occurred despite the fact that serial tracings were available before and after the development of the infarct.

A QRS-T pattern that was considered diagnostic of posterior infarction was found terminally in Lead aV_F of one patient with hemopericardium due to dissecting aneurysm.

Esophageal leads were obtained in five patients and were considered diagnostic of the posterior infarct found at autopsy.

Recent posterior infarction was generally manifested by reciprocal changes in the RS-T segment of precordial leads when the anterior wall was intact, but not when the anterior wall was infarcted.

Standard Leads II and III failed to provide diagnostic evidence of posterior infarction in cases where Lead aV_F was negative. Furthermore, the application of the Pardee criteria to the interpretation of the findings in the standard leads led to errors in a number of cases where correct diagnoses could be made from the findings in Lead aV_F .

REFERENCES

1. Pardee, H. E. B.: The Significance of an Electrocardiogram With a Large Q in Lead III, *Arch. Int. Med.* 46:470, 1930.
2. France, R.: The Large Q Wave in Lead III of the Electrocardiogram, *Am. J. M. Sc.* 187:16, 1934.
3. Durant, T. M.: The Initial Ventricular Deflection of the Electrocardiogram in Coronary Disease, *Am. J. M. Sc.* 188:225, 1934.
4. Wallace, A. W.: The Q Wave in the Electrocardiogram, *Am. J. M. Sc.* 188:498, 1934.
5. Bayley, R. H.: The Significance of the Duration of Q_3 With Respect to Coronary Disease, *AM. HEART J.* 18:308, 1939.
6. Schlomka, G., and Dressen, N.: Untersuchungen über die physiologische Unregelmässigkeit des Herzschlages; über die respiratorischen Schwankungen der Q_3 -Zacke des Elektrokardiogramms, *Ztschr. f. Krieslaufforsch.* 31:46, 1939.
7. Mazer, M., and Reisinger, J. A.: Criteria for Differentiating Deep Q_3 Electrocardiograms From Abnormal and Normal Cardiac Subjects, *Am. J. M. Sc.* 206:48, 1943.
8. Lyle, A. M.: Further Observations on the Deep Q_3 of the Electrocardiogram, *AM. HEART J.* 28:199, 1944.

9. Massie, E.: Discussion of paper entitled, "The Use of the Augmented Unipolar Left Leg Lead in the Differentiation of the Normal From Abnormal Q Wave in Standard Lead III," J. Lab. & Clin. Med. 30:347, 1945.
10. Ungerleider, H. E., and Gubner, R.: The Q_s and QS₃ Deflections in the Electrocardiogram; Criteria and Significance, AM. HEART J. 33:807, 1947.
11. Myers, G. B., and Oren, B. G.: The Use of the Augmented Unipolar Left Leg Lead in the Differentiation of the Normal From Abnormal Q Wave in Standard Lead III, AM. HEART J. 29:708, 1945.
12. Hamilton, J. G. M., and Nyboer, J.: The Ventricular Deflection in Myocardial Infarction—An Electrocardiographic Study Using Esophageal and Precordial Leads, AM. HEART J. 15:414, 1938.
13. Kossman, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction, AM. HEART J. 18:344, 1939.
14. Goldberger, E.: The Use and Advantages of Augmented Unipolar Extremity Leads (aV Leads) in the Electrocardiographic Diagnosis of Myocardial Infarction, New York State J. Med. 43:961, 1943.
15. Goldberger, E.: The Differentiation of Normal From Abnormal Q Waves, AM. HEART J. 30:341, 1945.
16. Myers, G. B., Klein, H. A., and Stofer, B. E.: I. Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction, AM. HEART J. 36:535, 1948.
17. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Infarction of the Intraventricular Septum and Right Ventricle, AM. HEART J. 37:720, 1949.
18. Dressler, W., and Roesler, H.: High T Wave in the Earliest Stage of Myocardial Infarction, AM. HEART J. 34:627, 1947.
19. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Advances in Internal Medicine 2:1, 1947, Interscience Publishers, New York, N. Y.
20. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Anterolateral Infarction, AM. HEART J. 36:838, 1948.
21. Hamburger, M., and Ferris, E. B.: Dissecting Aneurysm, AM. HEART J. 16:1, 1938.
22. Bayley, R. H., and Monte, L. A.: Acute, Local, Ventricular Ischemia, or Impending Infarction, Caused by Dissecting Aneurysm, AM. HEART J. 25:262, 1943.
23. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent Potential Variations of a Single Electrode, AM. HEART J. 9:447, 1934.
24. Goldberger, E.: A Simple, Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented, Unipolar, Extremity Leads, AM. HEART J. 23:483, 1942.
25. Wilson, F. N., et al.: The Precordial Electrocardiogram, AM. HEART J. 27:19, 1944.
26. Myers, G. B., and Klein, H. A.: The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads, AM. HEART J. 35:727, 1948.
27. Myers, G. B., Klein, H. A., and Hiratzka, T.: III. Correlation of Electrocardiographic and Pathologic Findings in Anteroposterior Infarction, AM. HEART J. 37:205, 1949.

POSITION OF PRECORDIAL LEADS

AN ANATOMICAL STUDY

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PRIOR to 1938, considerable variation and confusion existed in this country and abroad in the placement of precordial leads. In that year a joint committee of the American and British Heart Associations suggested the positions of the six precordial leads which are now in general use.¹ Wilson and associates² in experiments on dog hearts laid the groundwork for the present interpretation of normal precordial tracings. Direct leads were obtained from various areas and compared with tracings from overlying precordial positions. These in turn were compared with tracings made on human hearts from similarly placed electrodes and were found to be of essentially the same character. Although roentgenographic techniques have been used, nowhere in the literature have we been able to find anatomic correlation based on autopsy material.

It is generally considered that the dominant patterns obtained in precordial Leads 1 through 3 are produced in general by the electrical activity in the right ventricle, while Leads 4 through 6 reflect activity of the left ventricle. Experiments comparing direct epicardial leads in dog hearts with leads obtained from supra-adjacent chest areas show close similarity between precordial leads from Positions 1 through 3 and those leads in which the electrode is placed directly on the right ventricle. Similarly, precordial Leads 4 through 6 and direct left ventricular epicardial leads bear a resemblance in shape. This makes justifiable the general conclusion that, although subject to other influences, each lead largely records the electrical activity of the immediately underlying heart muscle.^{2,4} It has been found that leads from the right side of the precordium give complexes with small R and deep S waves, while leads from the left side give QRS complexes with tall R and small or absent S waves. Between these two opposites, with regard to the major deflections of the QRS complexes, lies an intermediate zone which yields intermediate complexes. This region has been named the "transitional zone." Among the several factors known to alter the position of the transitional zone are enlargement, displacement, and, perhaps most important, rotation of the heart. In some cases, the transitional zone cannot be defined by the area covered by the six standard precordial leads. This renders many electrocardiographic interpretations more difficult, since many diagnoses are based on the contrast between the left and right ventricular patterns.⁵

This study was undertaken to determine at autopsy, as accurately as possible, the areas of the heart explored by each precordial lead, and to correlate the position of the interventricular septum with the transitional zone. Normal and hypertrophied hearts were studied, the latter being divided into pure left hypertrophy, pure right hypertrophy, and combined ventricular hypertrophy.

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METHOD

A method of puncturing the chest wall was devised so that steel wires were introduced into the heart in areas corresponding to those covered by the standard precordial electrodes. For this purpose, a trocar was made with a circular metal disk attached perpendicularly to its long axis. Through this hollow guide, a second long trocar was threaded and wires were then introduced into the heart. Thus, any deviation of the trocars from the perpendicular was avoided. In precordial Positions 1 through 4, the needles were inserted perpendicularly to the chest wall. Wires were then left at the points of needle puncture until the heart was opened. In this way, there could be no doubt as to the portion of the ventricle immediately subjacent to the exploring precordial electrode. For precordial Positions 5 and 6, a slightly different procedure was adopted, for it was found that a needle introduced as described went posterior to the heart in a very high percentage of cases. This is true because the lateral chest wall is not parallel to the lateral border of the heart. Therefore, the trocar was inserted at a slight angle so that the nearest muscle mass was entered. It is recognized that departure from the perpendicular plane might introduce some uncertainty that the nearest heart area was always reached. Upon insertion of the trocar, the distance from the chest wall to the heart muscle was measured, and several angles of insertion were made to be sure that the nearest muscle mass was marked. In addition, repeated trials under direct vision on subjects with only the sternum removed showed that the use of a slight angle introduced only a minor error. Repeated punctures showed a variation of 0.5 to 1.0 cm. on the ventricular surface. In all cases, this proved to be the lateral or posterolateral wall of the left ventricle. In several cases of both normal and hypertrophied hearts, the so-called "auricular lead position,"⁵ that is, the third intercostal space just to the right of the sternum, was entered to determine if this position were truly an anatomic projection of the auricle.

The data so obtained were then transferred to an anatomic drawing of the heart which had previously been mimeographed (Fig. 1). This provided a graphic projection of the position of the precordial electrodes. Notation was made of the bodily habitus of the patient, the position of the diaphragm, and the position of the heart, whether vertical, intermediate, or transverse. Twenty-six cases were discarded because of confusing factors such as acute dilatation of the stomach and marked pneumothorax or hydropneumothorax which markedly disturbed the position of the heart after the electrocardiogram was taken. Cases of myocardial infarction, bundle branch block, or indefinite chamber hypertrophy were also discarded. The cases selected were clear cut, being either normal or with definite ventricular hypertrophy. It was felt unimportant to make an etiological distinction.

Although post-mortem changes in the size and shape of the heart may introduce some error of correlation with ante-mortem electrocardiograms, it is felt, after repeated observations, that such changes were minimal and did not invalidate the major conclusions. The only consistent change observed was that the diaphragm after death was slightly higher than during life.

As seen in the tables, each precordial lead position was correlated with the portion of the heart entered and the exact position of the septum noted. These data were then compared with the individual tracings of the corresponding six precordial (CF) leads. In those cases where the transitional zone was clearly defined by a definite shift in the major deflection, correlation was then made with the position of the septum.

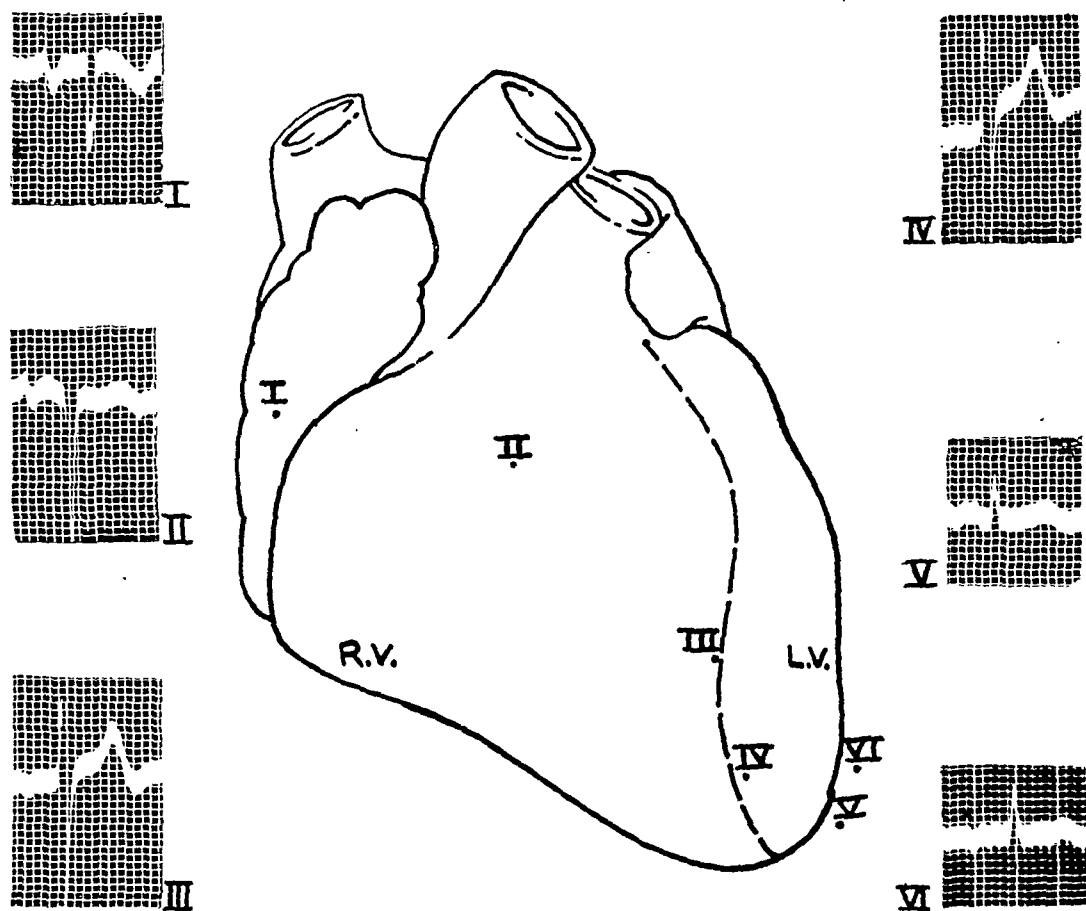


Fig. 1.—Case A-450. Normal heart with Lead CF₃ falling on the septum.

RESULTS

1. Auricular Lead.⁵—

Table I records the anatomic positions of the exploring trocar inserted into the heart through the third intercostal space at the right sternal border. It is seen that in this special auricular lead recommended by Graybiel and White,⁵ the exploring electrode was found to be over the upper pole of the right auricle in 80 per cent of the subjects. However, when the precordial position of Lead CF₁ was used, the trocar was found to enter the auricle in *all* cases. Anatomically at least, this position is well placed to serve as an auricular lead (Fig. 1).

TABLE I. THE ANATOMIC POSITIONS OF THE "AURICULAR LEAD POSITIONS" COMPARED WITH CF₁

CASE	TYPE OF HEART	"AURICULAR LEAD"	CF ₁	CASE	TYPE OF HEART	"AURICULAR LEAD"	CF ₁
224	Normal	R.A.	R.A.	221	L.V.H.	R.A.	R.A.
291	Normal	R.A.	R.A.	273	L.V.H.	S.R.A.	R.A.
241	Normal	R.A.	R.A.	307	L.V.H.	R.A.	R.A.
265	Normal	R.A.	R.A.	254	L.V.H.	R.A.	R.A.
272	R.V.H.	S.R.A.	R.A.	232	C.V.H.	S.R.A.	R.A.
226	R.V.H.	R.A.	R.A.	300	C.V.H.	R.A.	R.A.
225	R.V.H.	S.R.A.	R.A.	271	C.V.H.	R.A.	R.A.
303	R.V.H.	R.A.	R.A.	255	C.V.H.	R.A.	R.A.
				266	C.V.H.	R.A.	R.A.

R.V.H., Right ventricular hypertrophy.
L.V.H., Left ventricular hypertrophy.
R.A., Right auricle.

S.R.A., Superior to right auricle.
C.V.H., Combined ventricular hypertrophy.

2. *Normal Hearts.*—In nine cases (Table II), the position of the septum fell in the area between the precordial Positions 2 to 4 (Figs. 1 and 2). The average position was subjacent to precordial Position 3. The position of the heart had no constant effect on the position of the septum, although in most of the cases the hearts were intermediate in position. The transitional zone of the electrocardiogram was present between precordial leads made at Positions 3 and 4 to 5 with the average transitional zone being present in leads made between Positions 3 and 4. In all cases, therefore, there was at the most one lead space variation between the transitional zone of the electrocardiogram and the anatomic position of the septum.

TABLE II. NORMAL HEARTS. THE ANATOMIC POSITION OF THE RIGHT ATRIUM, THE VENTRICLES, AND THE SEPTUM IN RELATION TO THE ELECTROCARDIOGRAPHIC PRECORDIAL POSITION

CASE	WEIGHT (GRAMS)	THICKNESS OF VENTRICLES (CM.)		PRECORDIAL POSITIONS						HEART POSITION	T ZONE (ELECTRO-CARDIO-GRAPHIC PRE-CORDIAL POSITIONS)	SEPTUM (ELECTRO-CARDIO-GRAPHIC PRE-CORDIAL POSITIONS)
		R.V.	L.V.	1	2	3	4	5	6			
224	250	0.3	1.0	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	4-5	3-4
199	320	0.3	1.3	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Vertical	3	3-4
175	270	0.3	1.0	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3
291	300	0.2	1.2	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3
241	300	0.3	1.3	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Mid	3	2-3
139	310	0.3	1.4	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	4-5	3-4
205	310	0.5	1.3	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3
450	300	0.3	1.2	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3-4
498	320	0.4	0.8	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	4	3-4

R.V., Right ventricle.
L.V., Left ventricle.
T Zone, Transitional zone.

R.A., Right auricle.
S., Septum.

3. *Hearts With Left Ventricular Hypertrophy.*—In thirteen cases (Table III), the position of the anatomic septum varied between precordial Positions 2 and 4, with the average falling between Positions 3 and 4 (Figs. 2,c and 3). Again no

consistent relation was noted between the heart position and the location of the septum. The transitional zone of the electrocardiogram extended from precordial Lead 3 to Lead 4. The correlation with the anatomic transitional zone is thus seen to be one lead space.

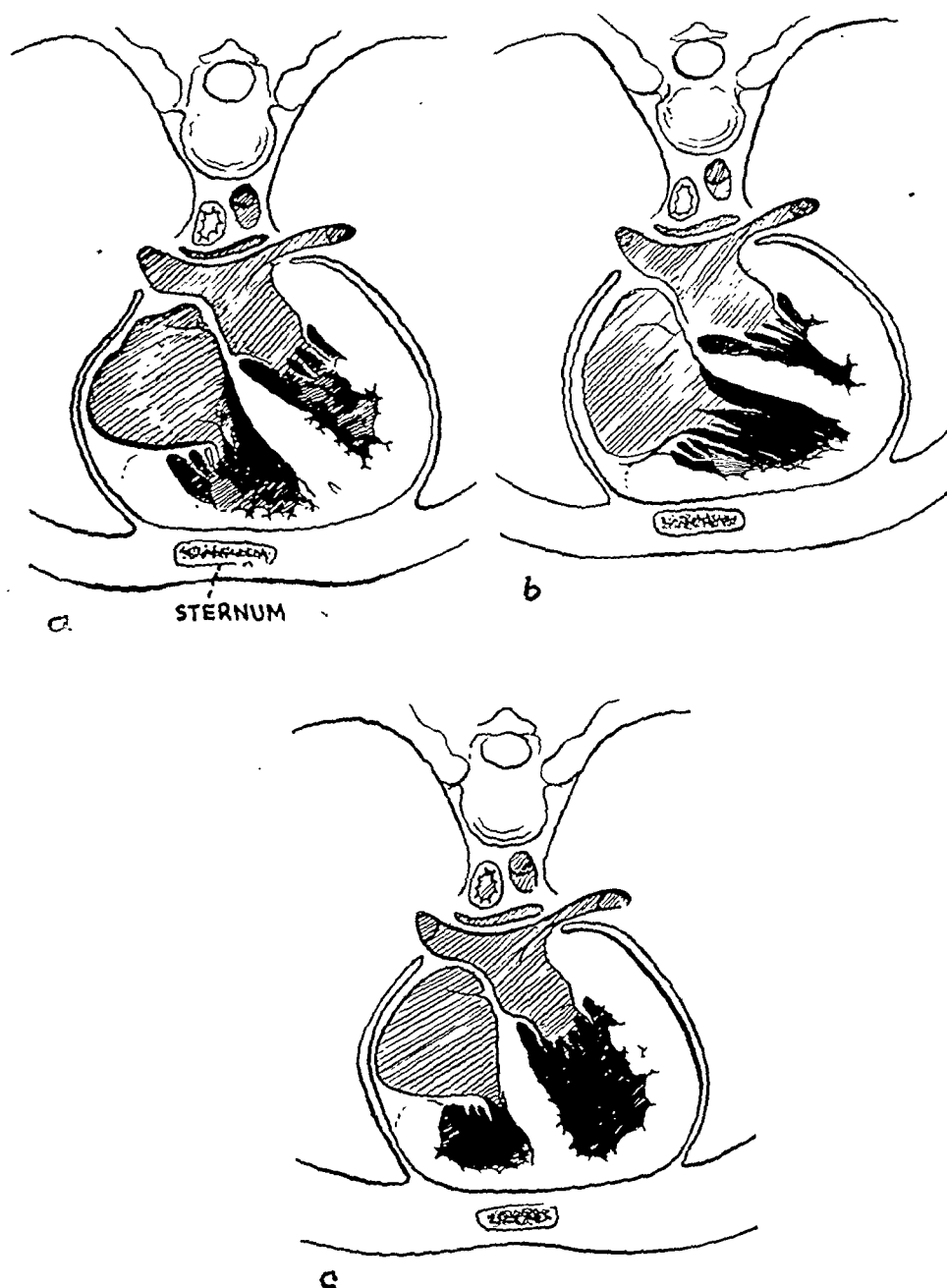


Fig. 2.—Sagittal section of a heart showing the anatomic relationship of the heart septum, chambers, ventricular walls, and thoracic structures.

a, Sagittal section of a normal heart showing oblique position of the septum with respect to the anterior chest wall. It is postulated that this relationship holds true for hearts with right ventricular hypertrophy without rotation (Case A-231); and for hearts with combined ventricular hypertrophy without preponderance of either ventricle (Case A-132).

b, Case A-272. Sagittal section through a heart with marked right ventricular hypertrophy showing rotation of ventricles so that the right lies anteriorly and the left moves posteriorly. This brings the septum into a plane nearly parallel to the anterior chest wall.

c, Case A-496. This heart had considerable left ventricular hypertrophy and a resultant shift of the septum into a plane nearly perpendicular to the anterior chest wall.

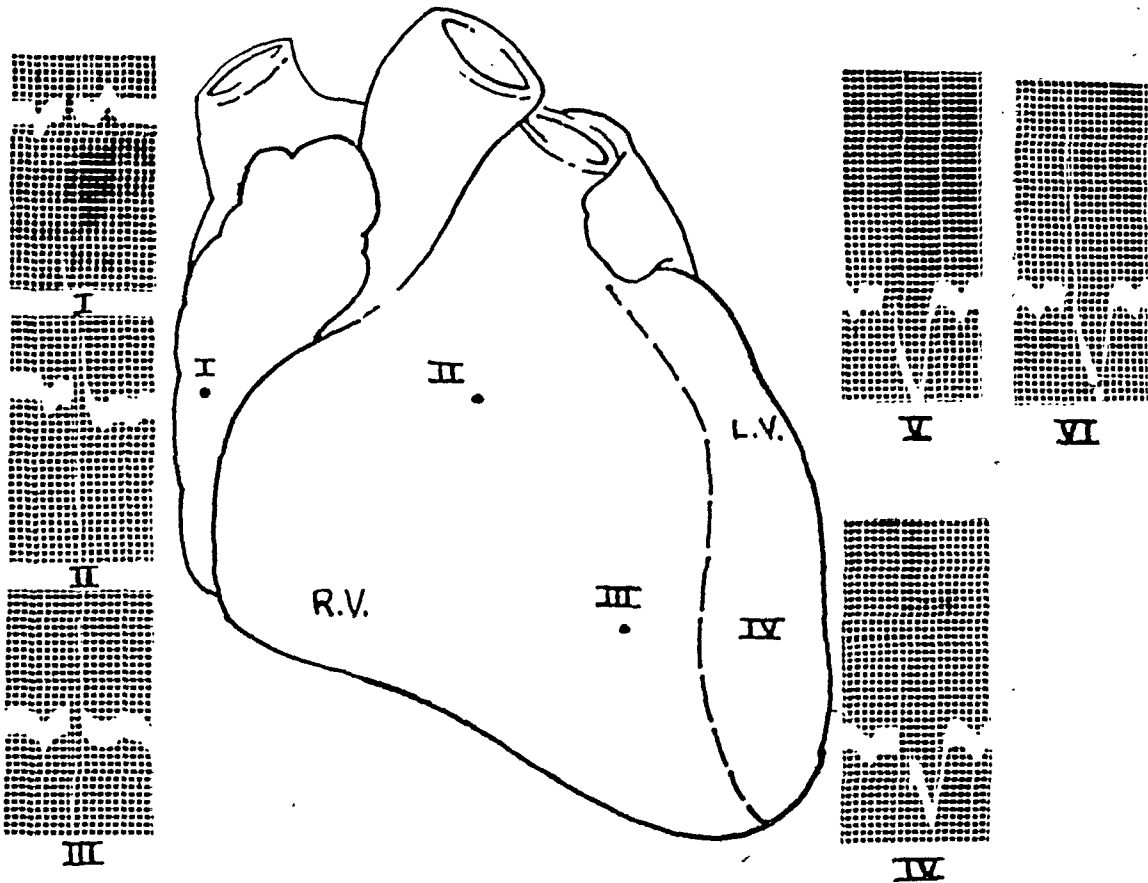


Fig. 3.—Case A-496. Heart with left ventricular hypertrophy. The septum falls between Leads CF₃ and CF₄. The transitional zone of the electrocardiogram is very sharp. Other cases showed the septum subjacent to Lead CF₄. Hypertrophy of the left ventricle is mainly to the left and posterior.

TABLE III. HEARTS WITH LEFT VENTRICULAR HYPERTROPHY. THE ANATOMIC POSITION OF THE RIGHT ATRIUM, THE VENTRICLES, AND THE SEPTUM IN RELATION TO THE ELECTROCARDIOGRAPHIC PRECORDIAL POSITION

CASE	WEIGHT (GRAMS)	THICKNESS OF VENTRICLES (CM.)		PRECORDIAL POSITIONS						HEART POSITION	T ZONE (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POSITIONS)	SEPTUM (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POSITIONS)
		R.V.	L.V.	1	2	3	4	5	6			
182	480	0.2	1.8	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3
307	450	0.3	2.0	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Transverse	3	3-4
329	650	0.3	1.6	R.V.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	3	3-4
427	450	0.3	1.4	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	4	3-4
273	380	0.3	1.5	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Vertical	3	3-4
221	480	0.4	1.9	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Transverse	3	2-3
471	500	0.4	1.4	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	4	3-4
390	380	0.3	1.5	R.A.	R.V.	R.V.	S.	L.V.	L.V.	Mid	3	4
439	440	0.4	1.4	R.A.	R.V.	R.V.	S.	L.V.	L.V.	Transverse	3	4
132	500	0.4	2.0	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Transverse	3-4	3-4
187	640	0.4	2.0	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Transverse	3	2-3
321	360	0.2	1.5	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	4	3
254	500	0.3	1.5	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	None	3-4

R.V., Right ventricle.
L.V., Left ventricle.
T Zone, Transitional zone.

R.A., Right auricle.
S., Septum.

4. *Hearts With Right Ventricular Hypertrophy.*—In nine cases (Table IV) the anatomic septum ranged from precordial Position 2 to 3 to Position 4 to 5. In the average cases the septum fell beneath Position 3 (Figs. 2, *a* and *b*, 4, and 5). The position of the heart was most often vertical, but this was not true in three

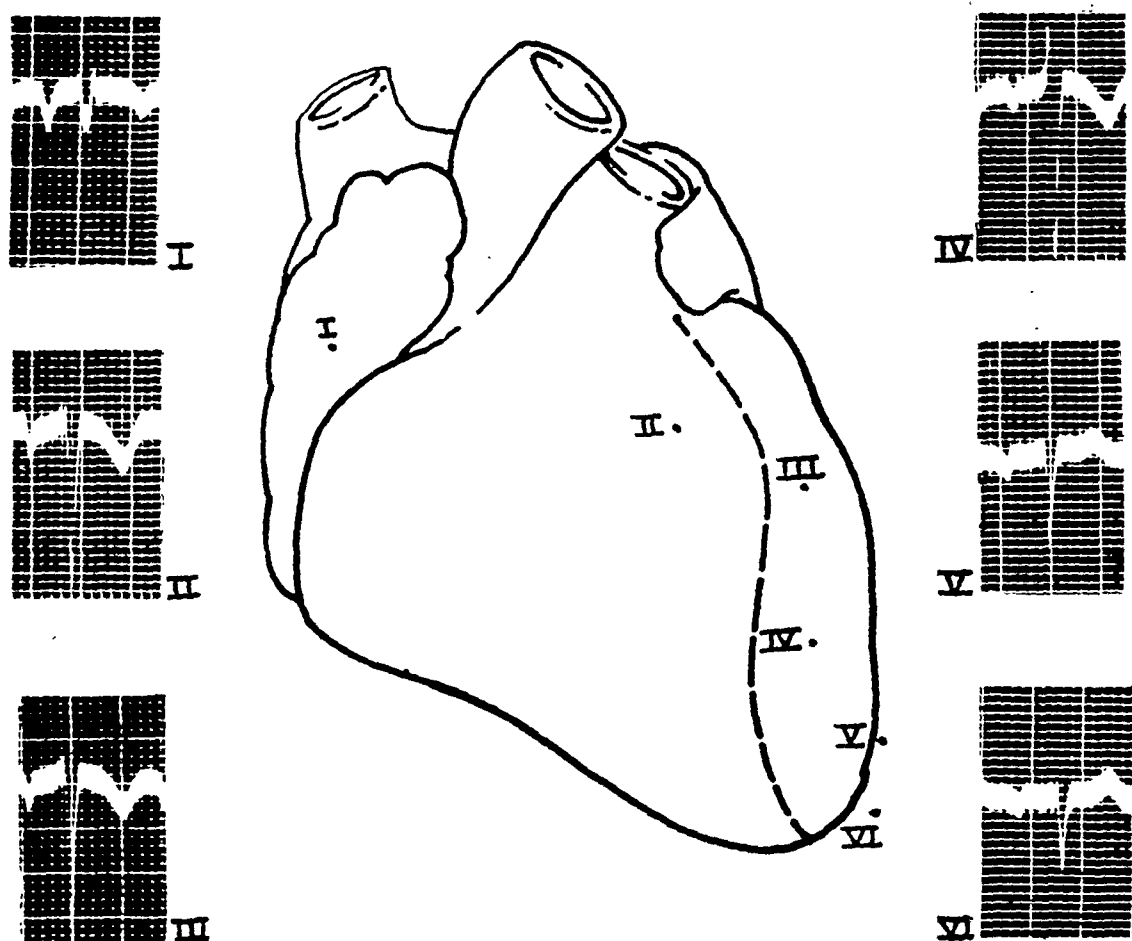


Fig. 4.—Case A-272. Heart with right ventricular hypertrophy. The heart lies in the vertical plane and has rotated counterclockwise as viewed from the base. The right ventricle is anterior, the left is posterior. No transitional zone is seen in the standard precordial electrocardiogram.

cases. The location of the transitional zone was not always revealed by the customary six precordial leads, but when it was present, it fell between precordial Leads 3 and 4 to 5. In three cases studied which displayed a transitional zone in the electrocardiogram, the correlation with the anatomic septum was absolute. In six cases, however, no transitional zone was seen.

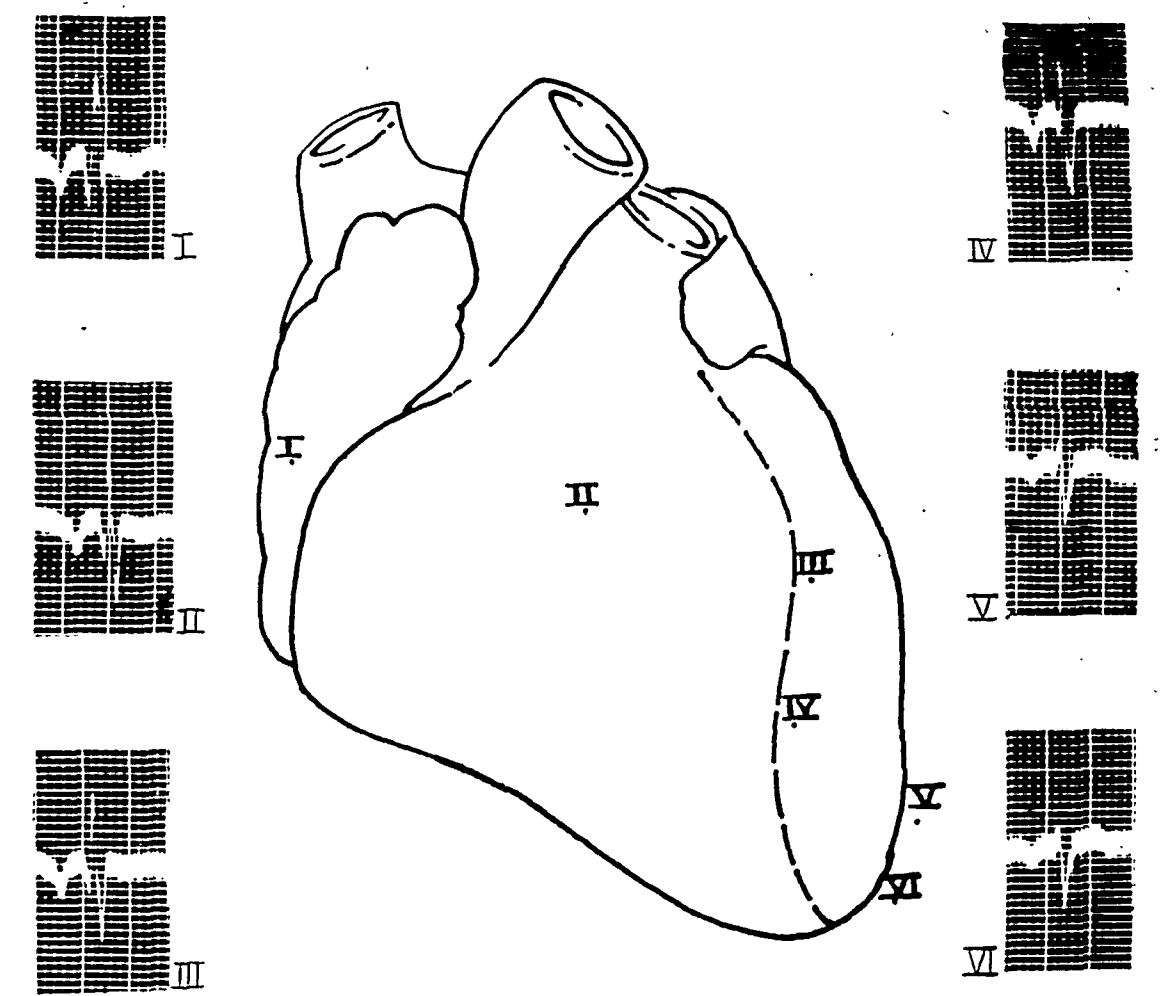


Fig. 5.—Case A-231. Heart with right ventricular hypertrophy. The heart is vertical in position but has not rotated to the same degree as the heart shown in Fig. 4. Electrocardiogram shows evidence of right ventricular hypertrophy.

TABLE IV. HEARTS WITH RIGHT VENTRICULAR HYPERTROPHY. THE ANATOMIC POSITION OF THE RIGHT ATRIUM, THE VENTRICLES, AND THE SEPTUM IN RELATION TO THE ELECTROCARDIOGRAPHIC PRECORDIAL POSITION

CASE	WEIGHT (GRAMS)	THICKNESS OF VENTRICLES (CM.)		PRECORDIAL POSITIONS						HEART POSI- TION	T ZONE (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POSI- TIONS)	SEPTUM (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POSI- TIONS)
		R.V.	L.V.	1	2	3	4	5	6			
170	400	0.7	1.3	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Vertical	None	2-3
303	450	0.7	1.2	R.A.	R.V.	R.V.	R.V.	L.V.	L.V.	Vertical	4-5	4-5
225	380	0.5	1.2	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Mid	None	2-3
226	350	0.6	1.2	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Vertical	None	3
140	350	0.5	1.0	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Mid	None	2-3
272	480	1.0	1.3	R.A.	R.V.	S.	S.	L.V.	L.V.	Vertical	None	4
198	650	0.6	1.3	R.V.	R.V.	L.V.	L.V.	L.V.	L.V.	Vertical	None	2-3
231	425	1.2	1.3	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Vertical	3	2-3
400	550	1.5	1.0	R.A.	R.V.	R.V.	S.	L.V.	L.V.	Mid	4	4

R.V., Right ventricle.
L.V., Left ventricle.
T Zone, Transitional zone.

R.A., Right auricle.
S., Septum.

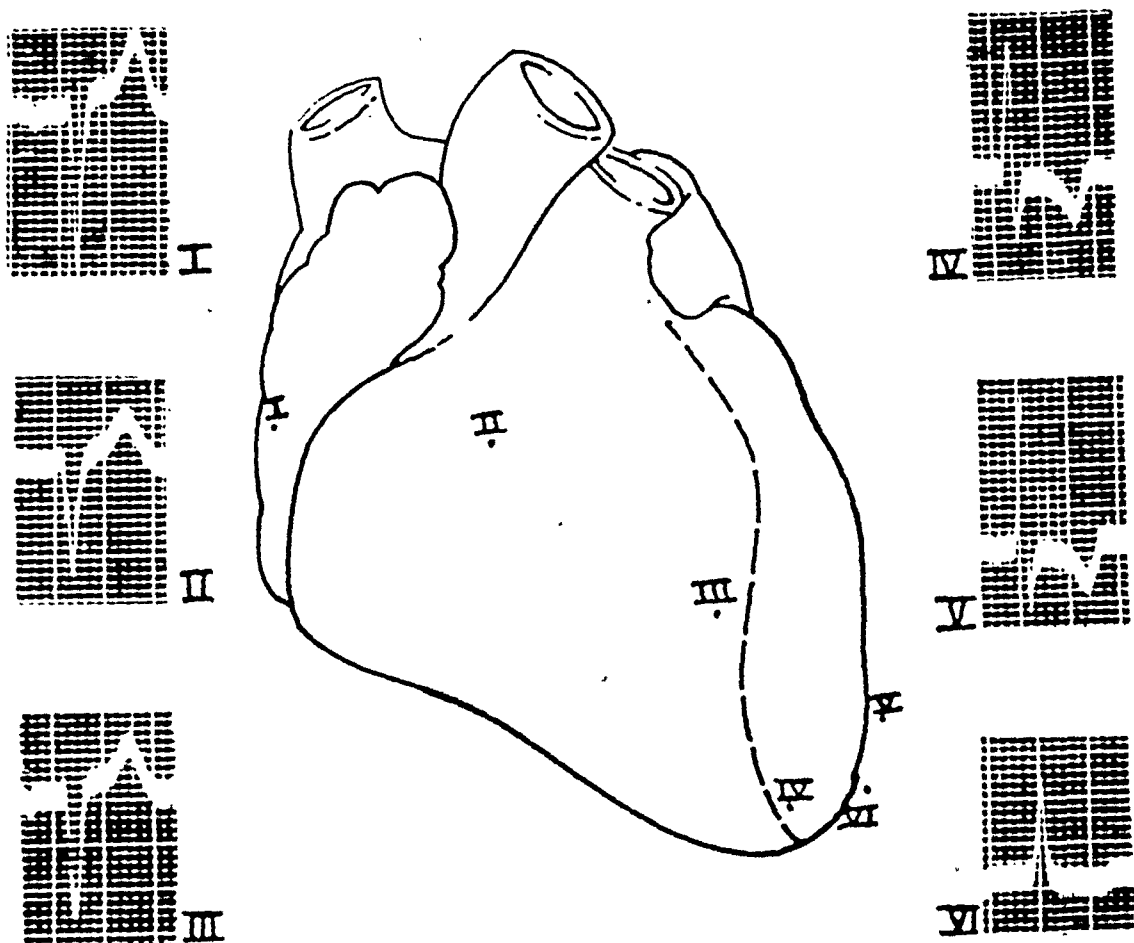


Fig. 6.—Case A-132. Heart with combined ventricular hypertrophy. In this case the septum falls between Leads CF_3 and CF_4 .

TABLE V. HEARTS WITH COMBINED VENTRICULAR HYPERTROPHY. THE ANATOMIC POSITION OF THE RIGHT ATRIUM THE VENTRICLES, AND THE SEPTUM IN RELATION TO THE ELECTROCARDIOGRAPHIC PRECORDIAL POSITION

CASE	WEIGHT (GRAMS)	THICKNESS OF VENTRICLES (CM.)		PRECORDIAL POSITIONS						HEART POSITION	T ZONE (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POS- ITIONS)	SEPTUM (ELECTRO- CARDIO- GRAPHIC PRE- CORDIAL POS- ITIONS)
		R.V.	L.V.	1	2	3	4	5	6			
297	560	0.5	2.0	R.A.	R.V.	R.V.	R.V.	L.V.	L.V.	Mid	4	4-5
396	440	0.5	1.7	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Mid	3	2-3
379	490	0.5	1.5	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Transverse	3	3-4
300	540	0.6	1.5	R.A.	R.V.	R.V.	R.V.	L.V.	L.V.	Transverse	4-5	4-5
322	400	0.5	1.4	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Mid	3	3-1
232	470	0.5	1.4	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3-4	3
283	680	0.5	2.1	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Transverse	3	3
160	400	0.5	1.5	R.A.	R.V.	R.V.	S.	L.V.	L.V.	Transverse	None	4
449	500	0.5	1.3	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Mid	3	2-3
483	500	0.5	1.3	R.A.	R.V.	R.V.	L.V.	L.V.	L.V.	Vertical	3-4	3-4
266	600	0.6	1.8	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	4	3
255	350	0.5	1.4	R.A.	R.V.	S.	L.V.	L.V.	L.V.	Mid	3	3
271	680	0.8	2.0	R.A.	R.V.	L.V.	L.V.	L.V.	L.V.	Vertical	4	2-3

R.V., Right ventricle.
L.V., Left ventricle.
R.A., Right auricle.

S., Septum.
T Zone, Transitional zone.

5. *Hearts With Combined Ventricular Hypertrophy.*—In thirteen cases (Table V) the anatomic range of the septum fell between Position 2 or 3 and Position 4 or 5 (Fig. 6). The average fell between precordial Positions 3 and 4. Again there was no correlation of the position of the heart with that of the septum. The transitional zone of the electrocardiogram ranged from precordial Lead 3 to Lead 4 to 5. The average fell between Leads 3 and 4. The correlation with the anatomic position was found to be very good. In only two cases did a considerable discrepancy exist. The correlation depended upon which ventricle was in preponderance, the left or the right, and upon which direction the septum rotated, vertically or transversely.

DISCUSSION

In brief, it may be seen that the six standard precordial lead positions in general use have been well selected in that the heart is explored from the right auricle to the left lateral ventricle. Although the auricular lead proposed by Graybiel and White⁵ is less influenced by ventricular activity than a precordial lead taken at Position 1, the latter will consistently overlie the right auricle.

The position of the septum cannot be assumed, even though the type of hypertrophy (right, left, or combined) is known, because of the existence of other factors, such as rotation, which may offset these influences. However, in general, the anatomic septum shifts slightly to the left in left hypertrophy (Fig. 3) and slightly to the right in right hypertrophy (Figs. 4 and 5). With combined hypertrophy the position is unpredictable, depending upon the dominant ventricle. This shift in cases with left ventricular hypertrophy is mirrored within one lead space by the transitional zone of the electrocardiogram. Unfortunately, the shift is not sufficiently marked to predict with any accuracy the type of hypertrophy present, but is in the same direction as the predominating ventricular pattern.

It is of interest to note that in normal hearts the septum lies at an oblique angle to the anterior chest wall (Fig. 2,*a*), whereas in marked left hypertrophy, it assumes an almost perpendicular position (Fig. 2,*c*). In marked right hypertrophy, it is generally conceded that the heart lies in a more central position and is rotated counterclockwise on its long axis as viewed from the base of the heart. When this occurs, the left ventricle lies almost completely posteriorly and the septum comes to lie in a plane nearly parallel with the anterior chest wall (Fig. 2,*b*). This explains the anatomic location of precordial Leads 3 through 6 in the narrow portion of the left ventricle presenting on the anterior surface (Fig. 4). Thus, it is believed that the presence or absence of a transitional zone is determined by the relative positions of the ventricles, or more simply, by the plane of the septum. In left hypertrophy the transitional zone is sharply demarcated and here the septum lies perpendicular to the precordium. In right hypertrophy, where the septum lies parallel to the anterior chest wall, the transitional zone is absent in the six standard precordial positions (Fig. 4). It is believed that the anatomic position of the septum explains those cases in which no transitional zone is seen in the standard precordial electrocardiogram. The degree and type of rotation of the heart influence the position of the septum more than actual

hypertrophy of the right ventricular wall. The frequent occurrence in right ventricular hypertrophy of vertical hearts, which have rotated counterclockwise as viewed from the base, will explain why transitional zones are so much more frequently absent in electrocardiograms taken in cases of cor pulmonale than in other pathologic conditions. This conforms to the present theories concerning the mean electrical axis where an upright deflection is produced as the wave of electrical activity approaches the anterior chest wall, and a downward deflection is produced when the wave of electrical activity proceeds away from the anterior chest wall.

SUMMARY

1. Correlation of the electrical pattern of the precordial electrocardiogram with the anatomic projections of the corresponding precordial electrodes was performed. This was done in forty-four autopsied subjects by the insertion of wires into the ventricular myocardium at each of the six precordial positions of the electrocardiogram. A comparison of the anatomic position of the septum with the electrical position of the transitional zone was then made, and some conclusions drawn regarding the meaning of the transitional zone.

2. The standard six precordial leads are well selected in that they span the anterior surface of the heart from precordial Position 1, which overlies the right auricle, to Position 6, which overlies the anterolateral portion of the left ventricle.

3. The anatomic position of the septum is well correlated with the position of the electrical transitional zone in normal hearts and in those with predominant left ventricular hypertrophy.

4. The shift in the position of the septum and, therefore, of the transitional zone is not of sufficient magnitude to identify specific ventricular hypertrophy.

5. Left ventricular hypertrophy produces a sharp transitional zone. This is believed to be due to the plane of the septum being perpendicular to the anterior chest wall.

6. Right ventricular hypertrophy often shows no transitional zone in the span of the standard six precordial electrodes. This is believed to be due to the transverse plane of the septum, produced by the fact that the anterior position of the right ventricle and the posterior position of the left ventricle cause the plane of the septum to be parallel to the anterior chest wall.

The authors are greatly indebted to Dr. Myron Prinzmetal for many ideas and suggestions in the pursuit of this investigation.

REFERENCES

1. Supplementary Report by the Committee of the American Heart Association for the Standardization of Precordial Leads, *AM. HEART J.* 15:235, 1938.
2. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
3. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, *Advances in Internal Medicine*, vol. 2, New York, 1947, Interscience Publishers, Inc., p. 25.
4. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, *Advances in Internal Medicine*, vol. 2, New York, 1947, Interscience Publishers, Inc., pp. 29-30.
5. Graybiel, A., and White, P. D.: *Electrocardiography in Practice*, ed. 2, Philadelphia, 1946, W. B. Saunders Company, p. 6.

Clinical Reports

PRIMARY AMYLOIDOSIS OF THE HEART

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PPRIMARY amyloidosis is a relatively rare condition of unknown etiology, characterized by deposits of an irregularly staining protein substance, usually in mesodermal organs, and by the absence of any preceding chronic suppurative or debilitating disease. Forty cases of primary amyloid disease have been completely reviewed up to 1945 by Koletsky and Stecher¹ and Lindsay and Knorp.² Since then seventeen additional cases³⁻¹³ have been reported, making a total of fifty-seven cases.

Post-mortem examinations have revealed that in 85 per cent¹¹ to 95 per cent¹ of the cases of primary amyloid disease there are deposits of amyloid in the heart. The occurrence of cardiac failure, however, has not been sufficiently emphasized. Over 50 per cent¹¹ of the patients initially show or ultimately develop the clinical picture of heart failure. The case to be reported is one in which there was a clinical picture of congestive heart failure of unknown etiology.

CASE REPORT

The patient, a 53-year-old-white man, was first seen on Aug. 13, 1945. His chief complaint was shortness of breath of one year's duration. In November, 1944, and in March, 1945, he had had several attacks of nausea, vomiting, weakness, and faintness. No pain was associated with these attacks. He noted progressive dyspnea, ankle edema, swelling of his abdomen, and occasional nocturia. In July, 1945, an abdominal paracentesis and two thoracenteses were done.

The past history disclosed that the patient had had a hemorrhoidectomy in 1938, and that since an attack of bronchopneumonia in 1925 he had tended to have frequent upper respiratory infections. There was no history of rheumatic fever, syphilis, or hypertension.

Physical examination revealed a small, well-developed and well-nourished man, who was moderately dyspneic. There was no adenopathy and no thyroid enlargement. The pupils were round and equal and reacted promptly to light and accommodation. Extraocular movements were normal. His mouth was edentulous; his tongue and throat showed no abnormality. The veins in his neck were distended. Chest examination revealed dullness, with absence of breath sounds and tactile fremitus over the right lung posteriorly up to the level of the inferior angle of the scapula. The left lung was resonant, with no abnormal findings. The heart was slightly enlarged to the left to percussion, with a soft systolic apical murmur that was not transmitted. Tones were of fair quality, eighty per minute, with an occasional extrasystole. Blood pressure was 155/85. The liver edge was palpable four fingerbreadths below the costal margin and was firm, smooth, and not tender. The spleen was not palpable. The abdomen was slightly distended, and shifting dullness was present. There was slight pitting edema of the ankles. The peripheral vessels were soft.

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Aided by the Louis M. Monheimer Memorial Fund.

On Aug. 14, 1945, the patient was admitted to the hospital and 1,500 c.c. of straw-colored fluid were removed from the right pleural cavity. The fluid on examination had a specific gravity of 1.009 and showed no malignant cells. The sediment consisted of polymorphonuclear leucocytes and lymphocytes.

The urine disclosed a trace of albumin and a 4 plus urobilinogen. While the patient was in the hospital the white count varied from 6,850 to 9,150, with 3 per cent eosinophiles, 3 per cent stab forms, 69 per cent segmented forms, 21 per cent lymphocytes, and 4 per cent monocytes. Hemoglobin was 93 per cent, with 4,840,000 red blood corpuscles. Prothrombin time was 75 per cent (Smith's Bedside Technique). Hematocrit was 50 per cent. Sedimentation rate was 4.0 mm. in one hour (Westergren). Fasting blood sugar was 90 mg. per cent, diastase 112, nonprotein nitrogen 19 to 21 mg. per cent. Icterus index was 10 and total proteins 6.3 grams, with albumin 5.0 grams and globulin 1.3 grams.

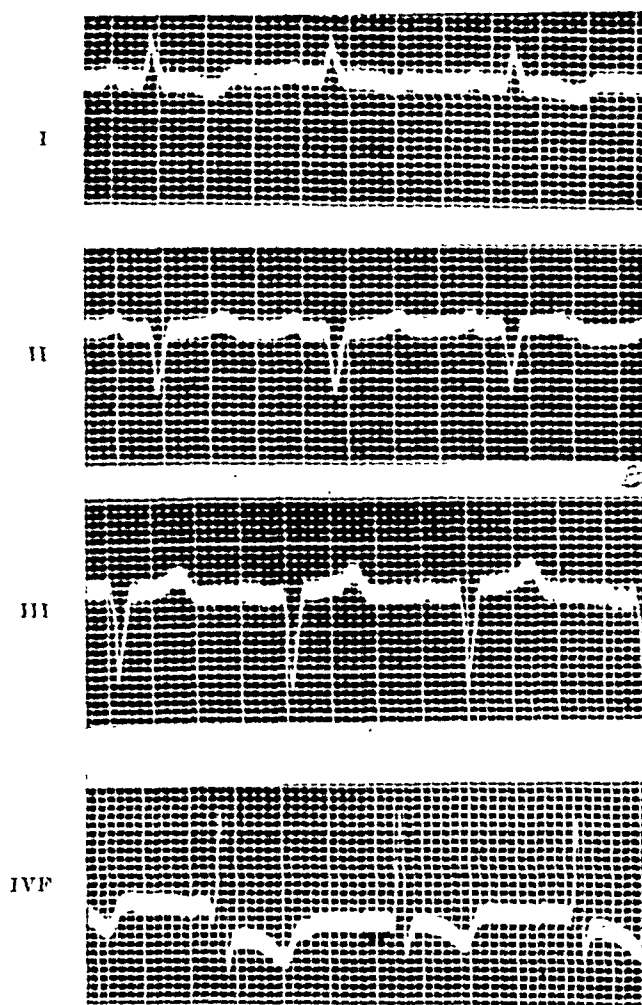


Fig. 1.—Electrocardiogram, Aug. 15, 1945.

The electrocardiogram taken on Aug. 15, 1945 (Fig. 1), showed the rhythm to be generally regular, interrupted by one premature nodal beat. The heart rate was 79 beats per minute. There was marked left axis deviation. The P-R interval measured 0.14 second. P waves were upright in the three conventional leads. QRS complexes were of normal duration and slurred in Lead I. T_1 was inverted; T_2 and T_3 were upright. In Lead IVF the Q waves were minute and absent, upright waves were dominant, and the T waves were inverted. The patient was receiving

two cat units of digitalis daily at this time. The electrocardiogram taken two weeks later showed less inverted T waves in Leads I and IVF. The P-R interval was 0.18 second.

The chest film showed a pleural effusion at the right base and the heart moderately enlarged to the left and right. Venous pressure on Aug. 16, 1945, was 24.5 cm. H₂O in the left antecubital vein. Arm-to-tongue time (Decholin) was thirty seconds; arm-to-lung (ether), eighteen seconds. The patient was digitalized, put on a low-salt diet, received ammonium chloride, and was given repeated injections of Mercupurin intravenously.

He required numerous thoracenteses, with from 1,100 to 2,000 c.c. of fluid being obtained at each tap. On Oct. 8, 1945, 1,100 c.c. were obtained from the right pleural cavity. The patient unexpectedly expired during the following night.

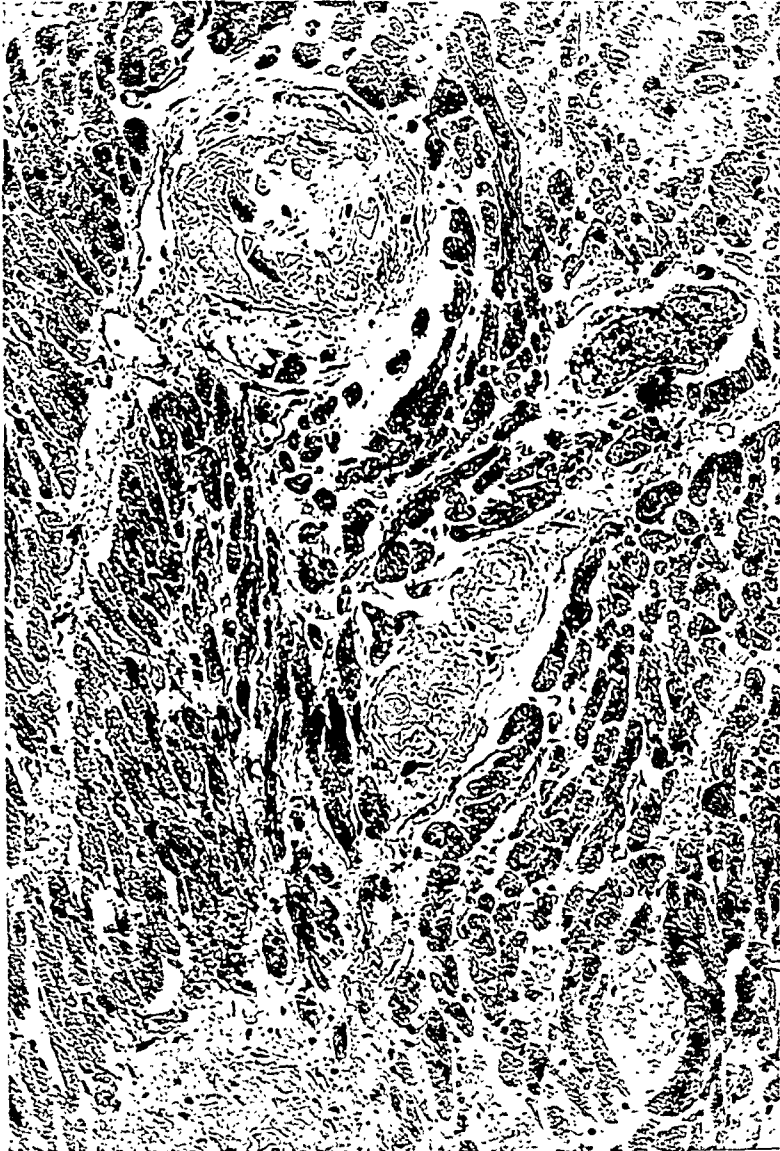


Fig. 2.—Section of heart showing masses of amyloid scattered through myocardium.

Autopsy.—There were 3,000 c.c. of straw-colored fluid in the peritoneal cavity, 400 c.c. in the right pleural cavity, and 50 c.c. in the pericardial cavity. The peritoneal, pleural, and pericardial surfaces were smooth and glistening.

The heart weighed 350 grams. The left and right ventricular walls were thick and the trabeculae were prominent. The mitral and aortic valves were thickened but intact. The coronary vessels were patent throughout and the foramen ovale was closed. The cardiac muscle showed a diffuse, yellow-grey mottling throughout and was of firm consistency. The lungs were crepitant throughout. In the left upper lobe was a well-encapsulated, hard, calcific nodule, about 0.5 cm. in diameter.

The spleen was of usual shape and size, and dark blue in color. The cut surface showed nothing remarkable. The gastrointestinal tract showed an intact mucosa and the walls were of unusual thickness. The liver was enlarged one and one-half times. On the cut surface the lobular picture was distinct, as a result of the presence of small, yellow foci in the center of the lobules. The renal capsules stripped with ease and the surfaces were smooth. The ratio of cortex to medulla was normal. The renal pelves were pale and smooth. The pancreas, biliary tract, adrenals, urinary bladder, and prostate showed nothing unusual. The cranial cavity was not examined.



Fig. 3.—Section of pancreas showing masses of amyloid deposited adjacent to vessels.

The organs when treated with iodine, followed by sulfuric acid, showed nothing unusual.

Microscopic Examination.—Sections were made and stained with hematoxylin-eosin, crystal violet, Congo red, and iodine. Homogeneous, structureless material, hereafter designated as amyloid, stained violet with crystal violet, but did not stain abnormally with the other dyes. Sections were also stained with Sudan IV.

Sections of the heart (Fig. 2) showed severe distortion of the usual pattern. Many muscle fibers had become atrophic or had disappeared. The interstitial tissue was greatly increased in amount and the vessels running through it were prominent. The wall of every individual vessel was thickened, as a result of the presence of large amounts of bluish-pink, structureless material (amyloid), which was also found in the immediate vicinity of the vessels and scattered throughout the myocardium. There was no inflammatory reaction in these vessels. The muscle fibers

showed linear droplets of fat adjacent to the nuclei. Small foci of amyloid were deposited in all of the valves.

Sections of the lungs showed marked dilatation of the vessels, particularly under the pleura. The parenchyma was not remarkable. In the alveoli there was an occasional macrophage containing brown pigment. The walls of the vessels showed, here and there, thickening and deposits of amyloid. Section of the spleen showed the malpighian bodies to be small, widely spread, and inactive. The sinusoids were distended with blood and their walls were delicate. Section of the liver showed dilated sinusoids, with the liver cords correspondingly narrowed, particularly around the central veins. There was a slight increase in the interstitial connective tissue and low-grade periportal infiltration by mononuclear leucocytes. A few of the larger vessels showed amyloid deposits in their walls. The liver cells surrounding the central veins had deposits of fat droplets. Section of the pancreas (Fig. 3) showed the acinar pattern preserved. The islets of Langerhans were scant. The pancreatic arteries showed large deposits of amyloid in their walls and occasionally in the adjacent parenchyma.

Section of the kidney showed the normal pattern preserved. The glomerular tufts and small vessels were distended with blood. The spaces of Bowman contained protein material, which was usually not very solid but which approached the consistency of amyloid in a few instances. The tubular epithelia were not very well preserved, showing granulation of the cytoplasm, but the basement membrane appeared of usual thickness. The lumina contained a hyaline cylinder here and there. A few scattered medium-sized vessels showed bluish-pink amyloid deposits in their walls and around one of these deposits two multinucleated giant cells were found.

The anatomical diagnoses were: primary amyloidosis of the myocardium, valves, and large vessels; hypertrophy of left and right cardiac ventricles; arteriosclerosis, slight; pleural effusion, right, 400 c.c.; chronic passive congestion of liver; congestion of spleen; and ascites, 3,000 cubic centimeters.

COMMENT

The patient presented the picture of progressive cardiac failure that did not respond to rest, digitalis, diet, and diuretics. The cause of the heart failure was not determined until post-mortem examination, when amyloid was found deposited throughout the myocardium and in all the valves of the heart. Since no associated disease was found, and the amyloid was confined to the cardiovascular system, this case is considered to be one of primary amyloidosis.

Amyloid disease is divided into four groups¹: (1) Secondary amyloidosis, (2) primary amyloidosis, (3) amyloid associated with multiple myeloma, and (4) tumor-forming amyloidosis. In secondary amyloidosis the deposits are usually present in the parenchymatous organs of the abdominal cavity, though other organs and tissues may also be affected. It is associated with prolonged suppuration or ulceration, such as tuberculosis, osteomyelitis, or syphilis.

Primary or atypical amyloidosis has the following characteristics:

1. Absence of preceding etiological factors such as tuberculosis or chronic suppuration.

2. Minimal involvement of organs usually affected in the secondary form, such as spleen, liver, and kidneys. Exceptions to this distribution have been reported.¹³⁻¹⁶

3. Maximal involvement of the cardiovascular system, gastrointestinal tract, smooth and striated muscle, and lymph nodes.

4. Atypical reactions of amyloid to the usual amyloid stains.

5. Tendency to nodular deposits.

From 6 per cent¹⁷ to 10 per cent¹⁸ of the cases of multiple myeloma are complicated by amyloidosis. The tumor form is quite rare, and in those cases the amyloid is deposited in the subcutaneous tissue and mucous membrane to form tumor masses.

The possibility of an ante-mortem diagnosis of primary cardiac amyloidosis is quite remote, because of the rarity of the condition and the lack of specific diagnostic aids. The disease could be clinically suspected in a person over 40 years of age who shows congestive heart failure, a normal or low blood pressure, and cardiac hypertrophy without apparent cause. In those cases in which electrocardiograms have been taken, low voltage and "myocardial damage" have been the common findings. Left axis deviation has occurred more commonly than right. Delayed A-V conduction,¹⁹ auricular fibrillation,²⁰ and premature contractions²⁰ have been reported.

Eisen¹¹ found in an analysis of the available laboratory data that a moderate hypochromic anemia and a moderately elevated sedimentation rate were consistent findings. In those cases reviewed by Eisen in which total proteins were obtained, the serum globulin was normal. Reversal of the albumen-globulin ratio in primary amyloidosis has since been reported in the cases of Ranström,⁶ Lindsay,⁹ and Iverson and Morrison.⁷

If a superficial structure such as the tongue, skin, or vagina is involved, a clinical impression of amyloidosis can be confirmed by biopsy. The Congo red test in primary amyloidosis is frequently negative. The dyspnea in amyloidosis may be difficult to evaluate. It may be caused by involvement of the heart, trachea, lungs, or mediastinum, or by the secondary anemia which is occasionally present.

SUMMARY

A case of primary amyloidosis of the myocardium, valves, and large vessels is presented. The patient showed progressive cardiac failure, which did not respond to treatment and ultimately led to death.

REFERENCES

1. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis; Involvement of Cardiac Valves, Joints and Bones, With Pathological Fracture of the Femur, *Arch. Path.* 27:267, 1939.
2. Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, *Arch. Path.* 39:315, 1945.
3. Golden, A.: Primary Systemic Amyloidosis of Alimentary Tract, *Arch. Int. Med.* 75:413, 1945.
4. Soisalo, P., and Ritama, V.: Zur atypischen Amyloidose mit besondere Berücksichtigung des Herzens, *Acta med. Scandinav.* 116:269, 1944.
5. Dirkse, Paul R.: Primary Amyloidosis of the Lungs, *Am. J. Roentgenol.* 56:577, 1946.
6. Ranström, S.: Amyloidosis Myocardii, *Acta med. Scandinav.* 123:111, 1946.
7. Iverson, Lalla, and Morrison, A. B.: Primary Systemic Amyloidosis, *Arch. Path.* 45:1, 1948.
8. Orloff, Jack, and Felder, Leonard: Primary Systemic Amyloidosis: Jaundice as a Rare Accompaniment, *Am. J. M. Sc.* 212:275, 1946.
9. Lindsay, Stuart: Primary Systemic Amyloidosis With Nephrosis, *Am. J. Med.* 4:765, 1948.
10. Weisman, R. E., Clagett, O. T., and McDonald, J. R.: Amyloid Disease of Lung Treated by Pneumonectomy, *J. Thoracic Surg.* 16:207, 1947.
11. Eisen, Herman N.: Primary Systemic Amyloidosis, *Am. J. Med.* 1:144, 1946.
12. Lindsay, Stuart: Heart in Primary Systemic Amyloidosis, *AM. HEART J.* 32:419, 1946.
13. Brown, H. A., and Selzer, G.: A Case of Primary Amyloidosis, *Clin. Proc.* 3:227, 1944.
14. Perla, D., and Gross, H.: Atypical Amyloid Diseases, *Am. J. Path.* 11:93, 1935.
15. Bannick, E. G., Berkman, J. M., and Beaver, D. C.: Diffuse Amyloidosis: Three Unusual Cases, *Arch. Int. Med.* 51:978, 1933.
16. Gerber, I. E.: Amyloidosis of the Bone Marrow, *Arch. Path.* 17:620, 1934.
17. Atkinson, F. R. B.: Multiple Myeloma, *M. Press.* 195:312 and 327, 1937.
18. Lichtenstein, Louis, and Jaffe, Henry L.: Multiple Myeloma, *Arch. Path.* 44:207, 1947.
19. Dillon, J. A., and Evans, L. R.: Primary Amyloidosis. Report of Three Cases, *Ann. Int. Med.* 17:722, 1942.
20. Larsen, R. M.: A Pathological Study of Primary Cardiac Amyloidosis, *Am. J. Path.* 6:147, 1930.

PENICILLIN THERAPY OF GONOCOCCIC ENDOCARDITIS

A CASE REPORT

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BACTERIAL endocarditis due to the gonococcus was generally recognized as being a highly fatal disease before the advent of antibiotic therapy. There have been few reports in medical literature concerning the use of penicillin in the treatment of this condition. Cecil¹ stated that the Committee on Chemotherapeutics and other agents of the Division of Medical Sciences of the National Research Council received reports of three patients with gonococcic endocarditis who were treated with penicillin. Two of these recovered, but no case abstracts were reported. Myers² recently reported a case of gonococcic endocarditis of the pulmonary valve with apparent cure eighteen months after penicillin therapy. However, bacteriologic evidence of gonococcic etiology in the latter case consisted only of recovery of gram-negative diplococci from empyema fluid and from vaginal secretions.

The following case of bacterial endocarditis was proved bacteriologically to be due to a gonococcus which was repeatedly isolated from blood cultures before the administration of penicillin.

CASE REPORT

A white merchant seaman, 20 years of age, was admitted to the hospital on May 19, 1947, complaining of headache and fever.

The patient stated that about seven days before admission, while at sea, he had developed general malaise, fever, and chills. The day after onset he had had a severe shaking chill followed by a high fever. This was associated with pain and swelling of his right ankle, which lasted for two days and then subsided. However, the fever continued, accompanied by heavy sweats, loss of appetite, and headache. The chief mate aboard ship prescribed aspirin and three to four tablets of a sulfonamide drug each day. The symptoms persisted and became increasingly severe. The patient was admitted to this hospital shortly after the arrival of his ship in Baltimore.

A review of the patient's past history revealed that he had had joint aches and pains at the age of 10 years. He stayed in bed for two weeks and recovered without apparent complications or subsequent recurrence. The patient contracted gonorrhea in March, 1946. He took tablets of one of the sulfonamides for two days, without relief, and then was hospitalized in Santos, Brazil, where he was given seven injections of penicillin. The urethral discharge promptly cleared and the patient had no recurrence. His last sexual intercourse prior to admission occurred in April, 1947. There was no history of urethral discharge or dysuria since his gonorrheal urethritis of March, 1946.

Physical examination revealed a well-developed, rather thin young man who was perspiring profusely and who appeared to be acutely ill. His temperature was 102.5° F., his pulse 92, his respiratory rate 20, and his blood pressure 110/58. Examination of the head and neck revealed nothing significant. Ophthalmoscopic examination showed normal eye grounds. The lungs were clear and resonant. The heart size and rhythm were within normal limits. A systolic thrill was

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palpated to the apex. A loud, harsh apical systolic murmur was heard, which was transmitted to the left axilla. The abdomen was soft and pliable. The liver was not enlarged. The spleen was readily palpated and slightly tender. The genitals were normal to inspection and palpation. Rectal digital examination was not done. The terminal phalanges of the fingers and toes showed definite clubbing. Neither lymphadenopathy nor petechiae were noted.

Laboratory Data.—Serologic tests for syphilis were negative. Agglutinations for typhoid "O" and "H," paratyphoid "A" and "B," *B. abortus*, and *Proteus* OX 19 were not significant. Four blood smears for malaria were negative. Urinalysis on admission showed a specific gravity of 1.016, sugar and albumin were negative, and microscopic examination showed one pus cast. The hemoglobin was 12 grams, the red blood count 3,150,000, and the white blood count 25,050, with 85 per cent neutrophils (21 stab forms) and 15 per cent lymphocytes.

On June 9, hemoglobin was 10 grams, red blood count 2,590,000, and white blood count 17,250, with 82 per cent neutrophils (16 stab forms) and 18 per cent lymphocytes. Urinalysis was normal except for microscopic findings of 10 to 15 red blood cells per high-power field. On June 18, hemoglobin was 12 grams, red blood count 3,320,000, white blood count 13,200, with 73 per cent neutrophils (13 stab forms) and 27 per cent lymphocytes. Urinalysis showed albumin, 10 mg. per cent, and 30 to 40 red blood cells per high-power field. On July 5, urinalysis showed albumin, 5 mg. per cent. Microscopic examination revealed 4 to 6 hyalin and finely granular casts per low-power field and 6 to 8 red blood cells per high-power field. On July 14, prostatic smear and culture showed no gonococci. On July 22, hemoglobin was 14.5 grams, white blood cell count 10,800 with a normal differential count, and the erythrocyte sedimentation rate was 14 mm. in one hour.

Eight blood cultures before specific therapy showed growths of gram-negative diplococci which grew in tryptose phosphate broth but did not grow in thioglycollate broth, after incubation for forty-eight hours. The organism grew on subculture to blood agar, "chocolate" agar, and phenol red agar with 20 per cent ascitic fluid. It was oxidase positive. No growth was noted on unenriched phenol red agar. These cultures were incubated in an atmosphere of carbon dioxide (candle jar method). At room temperature no growth occurred on enriched or unenriched media. The organism was agglutinated by the specific chicken antiserum of Phair.³ It fermented dextrose-producing acid and no gas, but split neither maltose nor sucrose. Bacteriologic evidence showed that this organism was *Neisseria gonorrhoeae*. This identification was confirmed by Dr. J. F. Mahoney, Director, United States Public Health Service Venereal Disease Research Laboratory, Stapleton, N. Y.

X-ray examination of the chest showed slight prominence of the lung root shadows. No recent infiltration was identified. The heart shadow was within the upper limits of normal size and showed evidence of some thickening of the left ventricle. The ascending section of the aorta was a little prominent. An intravenous pyelogram showed some enlargement of the right renal pelvis, which was about 2.0 by 3.0 cm. in size. There was a suggestion of an aberrant vessel at the right ureteropelvic junction. The kidneys were normal in position.

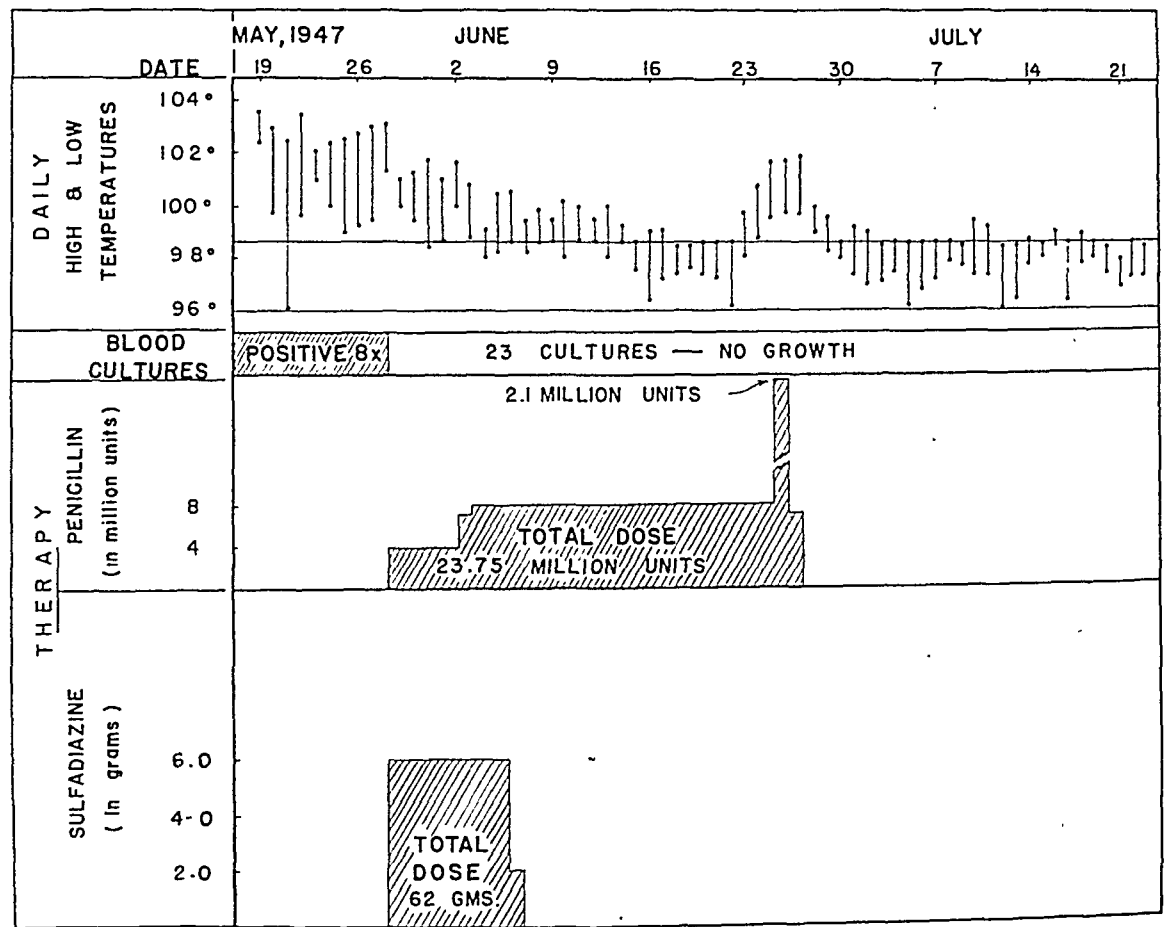
Twenty-three blood cultures obtained after specific therapy was begun showed no growth. Two gonococcus complement fixation tests on blood serum made on May 29 and June 3 were positive (1 plus). Two electrocardiograms were normal. The strain of *N. gonorrhoeae* which was isolated from blood cultures was completely inhibited in vitro by 0.125 unit per cubic centimeter of penicillin. The organism was somewhat resistant to sodium sulfadiazine and required a concentration of 40 mg. per cent to prevent growth.

Hospital Course.—The chart summarizes the patient's temperatures, blood cultures, and penicillin and sulfadiazine therapy from May 19 to July 24, 1947 (Fig. 1).

When admitted on May 19, the patient was acutely ill with high fever. Examination disclosed an enlarged, tender spleen, a systolic thrill and a murmur at the apex, and clubbing of the terminal phalanges of the fingers and toes. On May 22 he complained of sudden numbness of his right foot. The right dorsalis pedis and posterior tibial arteries were not palpable. Slight tenderness was noted in the right popliteal space. On May 24, the patient developed nausea, vomiting, and pain in the left upper abdominal quadrant. The spleen was larger and more tender. Nine days after admission, on May 28, the laboratory reported that a gram-negative diplococcus had been isolated from blood cultures. Penicillin and sulfadiazine therapy was begun. On May 29

the patient complained of pain and coldness of his left arm. The pulsations of the left axillary artery were palpated, but no pulsations of the left brachial and radial arteries were noted. Since the organism isolated from blood cultures showed a fairly high resistance in vitro to sulfadiazine, this drug was discontinued on June 7. The patient was given 2,500 c.c. of whole blood and ferrous sulfate during the latter part of his hospitalization for alleviation of his secondary anemia.

On June 15, seventeen days after specific therapy was begun, the patient's temperature became normal and remained so for eight days. Then a daily increase in temperature was noted for five days, reaching 101.8°F. (38.7°C.) on June 27. Because it was believed that this might be due to penicillin sensitivity, the penicillin was discontinued. Two days later the patient's temperature was within normal limits and he remained afebrile and asymptomatic during the remainder of his hospital stay. He was discharged on July 24, 1947, and was advised to return in three months for further study.



COURSE and THERAPY of a CASE of GONOCOCCIC ENDOCARDITIS.

Fig. 1

The patient was readmitted, for observation only, on Oct. 9, 1947. Since his previous discharge he had felt well and had gained weight. He complained only of some weakness and tiring of his right lower extremity on exercise. Physical examination disclosed the same harsh systolic precordial murmur, with radiation to the left axilla which had been noted previously. The left radial pulse was palpable but weaker than the right. A complete blood count was normal. The urine was normal. The sedimentation rate was 1.0 mm. in one hour. Three blood cultures showed no growth. X-ray examination of the chest showed no changes when compared with the film of May 20, 1947. The electrocardiogram was normal. The patient was discharged on Oct. 25, 1947, fit for duty.

He was again admitted on January 28, 1948, complaining of a penile sore which was diagnosed as a chancroid. Since his previous discharge he had felt entirely well except for occasional tiredness. Physical examination revealed nothing significant except for the presence of an ulcer near the frenulum of the penis, and, as had been noted before, a harsh apical systolic murmur and clubbing of the fingers and toes. Laboratory data showed the blood count, hemoglobin, and urine to be normal. A prostatic smear and culture showed no gonococci. Aerobic and anaerobic blood cultures showed no growth. Dark-field examination of material scraped from the penile lesion was negative for *Treponema pallidum*. The Ducrey intradermal skin test was positive and the Frei test was negative. The sedimentation rate was 1.0 mm. in one hour (Wintrobe). X-ray examination of the chest showed no changes since the previous examination. The electrocardiogram was normal. The patient was given 1.0 Gm. of sulfathiazole four times daily for five days. The penile lesion healed. He was discharged from the hospital on Feb. 6, 1948, in good condition.

COMMENT

This patient had gonococcic endocarditis, which was believed to be superimposed upon a deformed and incompetent mitral valve as the result of previous rheumatic heart disease. Previous rheumatic heart disease was indicated by his history of "joint trouble" at 10 years of age and the persistence throughout the period of observation of an apical thrill and a harsh systolic mitral murmur with radiation to the left axilla.

The diagnosis of gonococcic endocarditis was established by repeatedly positive blood cultures and the occurrence of embolic phenomena. Eight blood cultures made before specific therapy showed growths of gram-negative diplococci which were bacteriologically identified as being *N. gonorrhoeae*. In the acute stages of this patient's illness there were evidences of emboli to the right leg, left arm, and spleen.

Specific therapy consisted of 23.75 million units of penicillin and 62 Gm. of sulfadiazine. Because this strain of gonococcus was found to be moderately resistant to sulfadiazine, the drug was discontinued after ten days of treatment. Penicillin was continued for thirty-one days and then was stopped because of the development of fever, which was believed to be due to penicillin sensitivity.

This patient was followed for over seven months after discontinuance of antibiotic therapy, and no evidence of recurrence of gonococcic endocarditis was noted.

SUMMARY

1. A case of gonococcic endocarditis superimposed on a healed rheumatic mitral valve deformity is reported. The etiological diagnosis was confirmed by eight positive blood cultures of *N. gonorrhoeae* obtained prior to therapy.

2. Treatment with penicillin and sulfadiazine resulted in an apparent cure.

REFERENCES

1. Cecil, Russell L.: A Textbook of Medicine, ed. 7, Philadelphia, 1947, W. B. Saunders Company, p. 193.
2. Myers, Walter K.: Penicillin Therapy of Gonococcic Endocarditis of the Pulmonary Valve, J. A. M. A. 133:1205, 1947.
3. Phair, J. J., Smith, D. G., and Root, C. M.: Use of Chicken Serum in the Species and Type Identification of Neisseria, Proc. Soc. Exper. Biol. & Med. 52:72, 1943.

ELECTROCARDIOGRAMS OF AN UNUSUAL PATTERN IN A PATIENT WITH ANOMALOUS AURICULOVENTRICULAR EXCITATION

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SINCE it was shown that electrocardiograms with short P-R intervals and widened QRS complexes constituted part of a not infrequent syndrome,¹ the condition has received considerable attention. It is generally considered to be the result of activation of the ventricle through anomalous conduction pathways between the auricles and ventricles.

Electrocardiograms obtained from a young man who showed this disturbance intermittently will be presented. The unusual feature of the case was the instability of the disturbance.

CASE HISTORY

H. G., age 34, presented himself complaining of occasional stabbing pain in the region of his heart which recurred several times daily, lasted a few seconds, and was unrelated to effort. No other symptoms referable to the cardiovascular system were present. There was no disability. He passed a strenuous physical test as a line officer and campaigned actively overseas during World War II. The past history was essentially negative; there was no history of rheumatic fever or chorea.

Physical examination revealed nothing important. The patient was of medium body build. The blood pressure was 110/80. The cardiac rhythm was regular and the heart rate was 70 per minute. The heart size was normal. No thrills and no murmurs were detected. X-ray films of the chest showed normal lung fields and a normal cardiac silhouette. The blood count was normal. The sedimentation time was normal.

An electrocardiogram taken on the day of the initial examination (Fig. 1) revealed a Q_2 of 2.0 mm. which varied slightly with respiration, a Q_3 of 1.0 mm., an elevation of S-T₂ and S-T₃ of 1.0 mm., and inversion of T₃. In view of the history and the appearance of the first tracing, the patient was recalled for a second electrocardiogram on the following day. In this tracing (Fig. 2) there is seen a short P-R interval of 0.08 second in Lead I, of 0.12 second in Lead II, and of 0.16 second in Lead III. The QRS complex in Lead I is widened to 0.14 second, and the ascending limb is slurred. The QRS complex in Lead II measures 0.12 second with a notching of the ascending limb. The QRS complex in Lead III measures 0.10 second. There is a Q wave in Lead III of 5.0 mm. and an elevation of the RS-T in Lead III of 2.0 millimeters. The T waves are upright in the limb leads, inverted in Lead CF₃, and diphasic in Lead CF₄.

On comparing these tracings, one notes that the second tracing differs from the first by showing shortening of the P-R interval in Lead I, widening of QRS in Leads I and II, deepening of the Q wave in Lead III, and reversal of the direction of the T wave in Lead III and in the chest leads. In addition, there is a marked increase of amplitude of \bar{R} in Lead I and a decrease of R in Leads II and III.

The presence of anomalous A-V excitation of an unusual pattern was suggested by these findings, and three days after the second tracing additional electrocardiograms were made. Extremely long graphs were made with the intention of demonstrating, if possible, the shift from the normal to the abnormal pathway.

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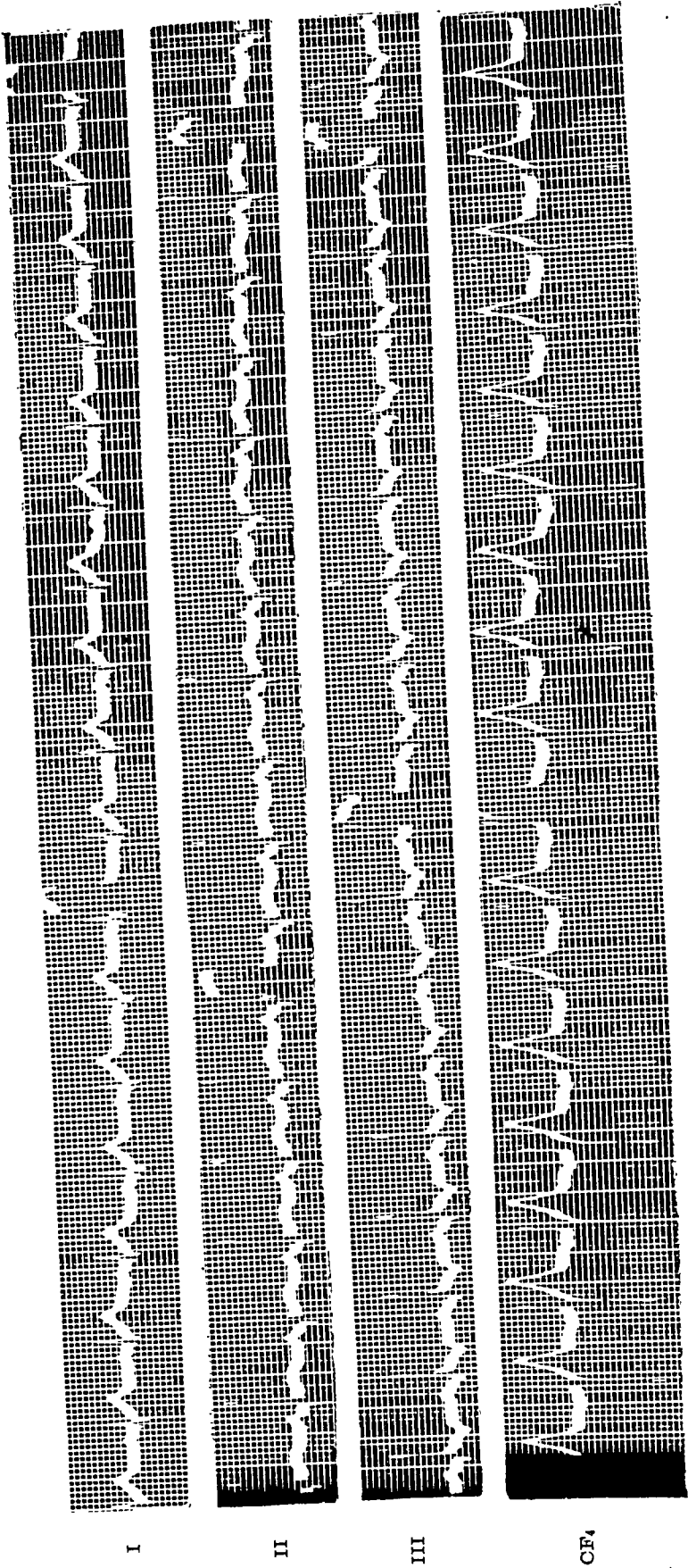


Fig. 1.—The electrocardiogram shows a normal A-V excitation.

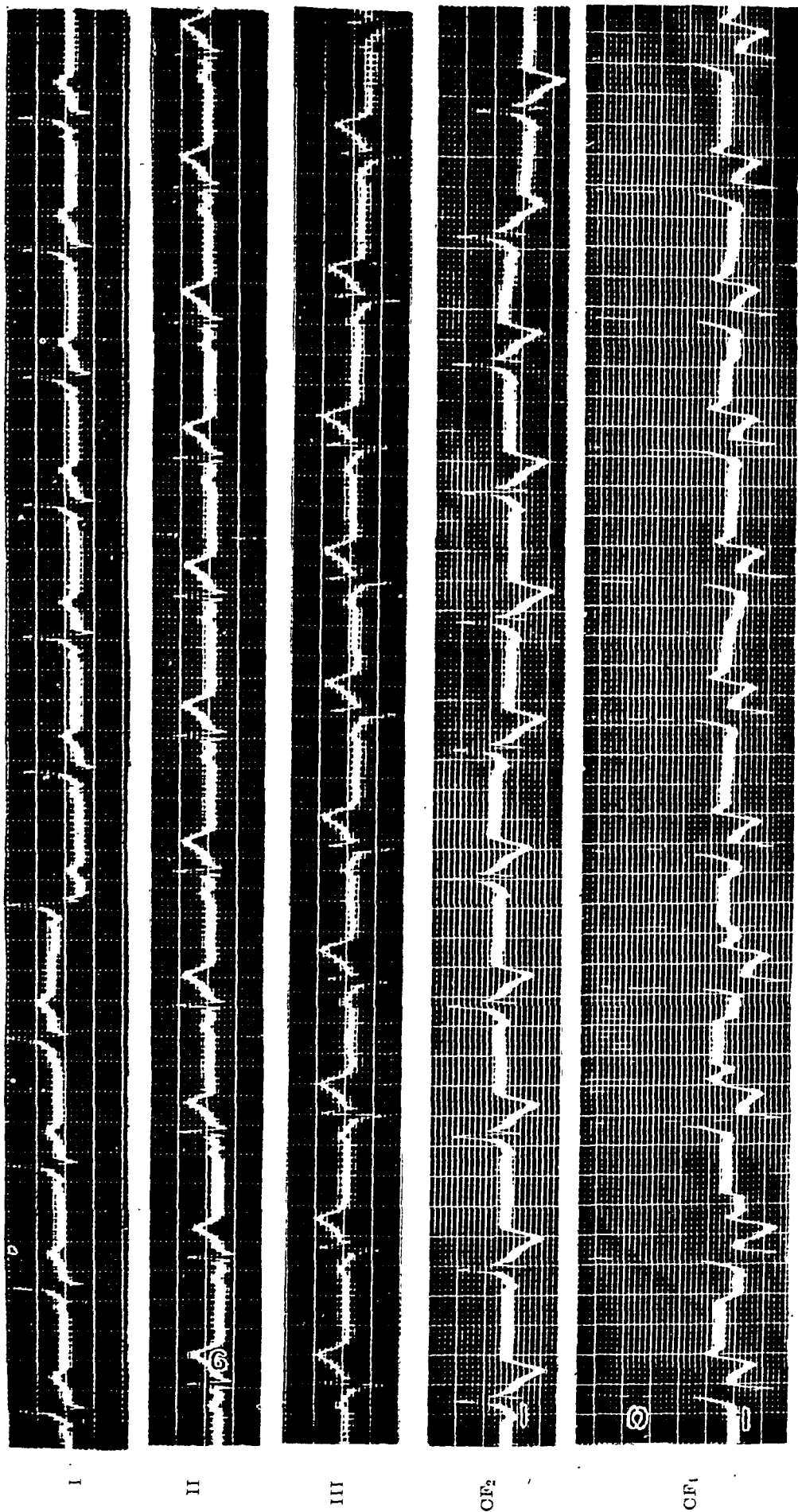


Fig. 2.—One day later the tracing shows a short P-R interval in Lead I, a widening of QRS in Leads I and II, a deepening of the Q wave in Lead III, and a reversal of the direction of the T wave in Lead III and in the chest leads.

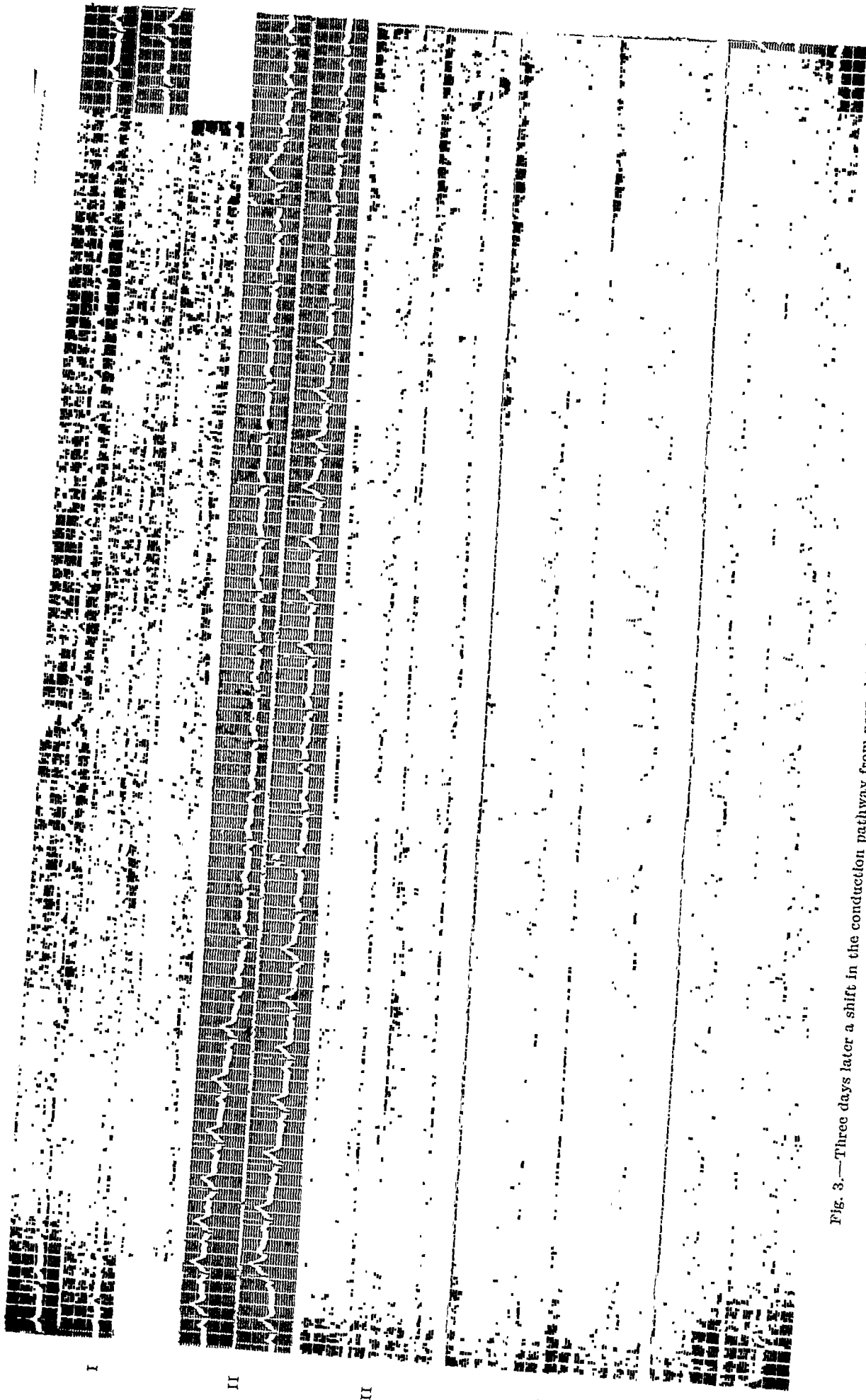


Fig. 3.—Three days later a shift in the conduction pathway from normal to abnormal to normal can be seen to take place many times.

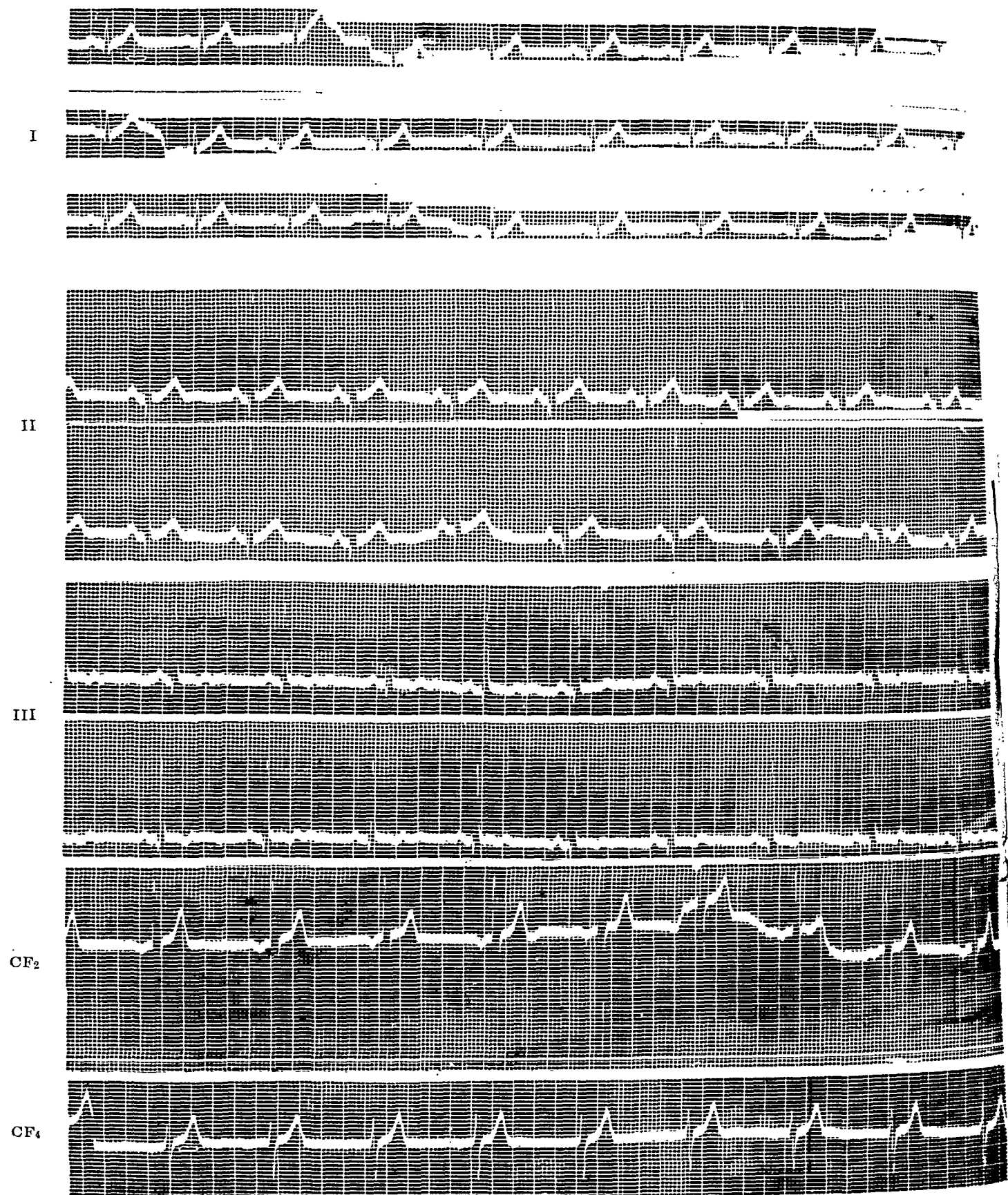


Fig. 4.—This tracing was taken less than one hour later. Normal A-V excitation is seen throughout.

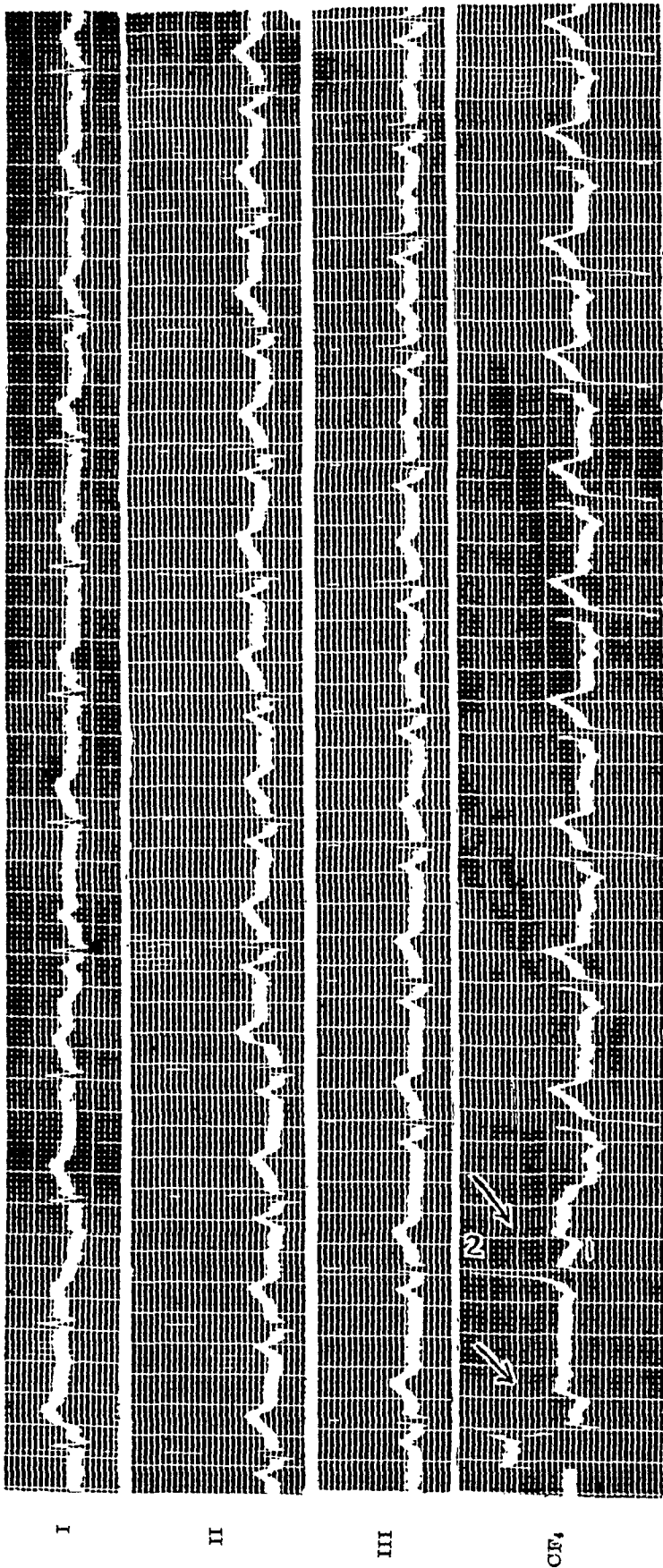


Fig. 5.—Maximal Inhalation. No effect on the duration of the P-R or QRS intervals is observed.

In Fig. 3, the unbroken graph of each lead is shown almost in its entirety. (A small part at the end of each lead is missing, to facilitate photography.) A shift in the conduction pathway from normal to abnormal to normal can be seen to take place many times. This shift occurred irregularly. A fourth series of leads were taken within the hour and in this tracing (Fig. 4) complexes exhibiting a normal conduction pathway appear throughout. Slight variation in amplitude of R_1 is due to difference in standardization. (Another instrument was employed.) Alteration in direction and amplitude of T_3 is thought to be due to respiration.

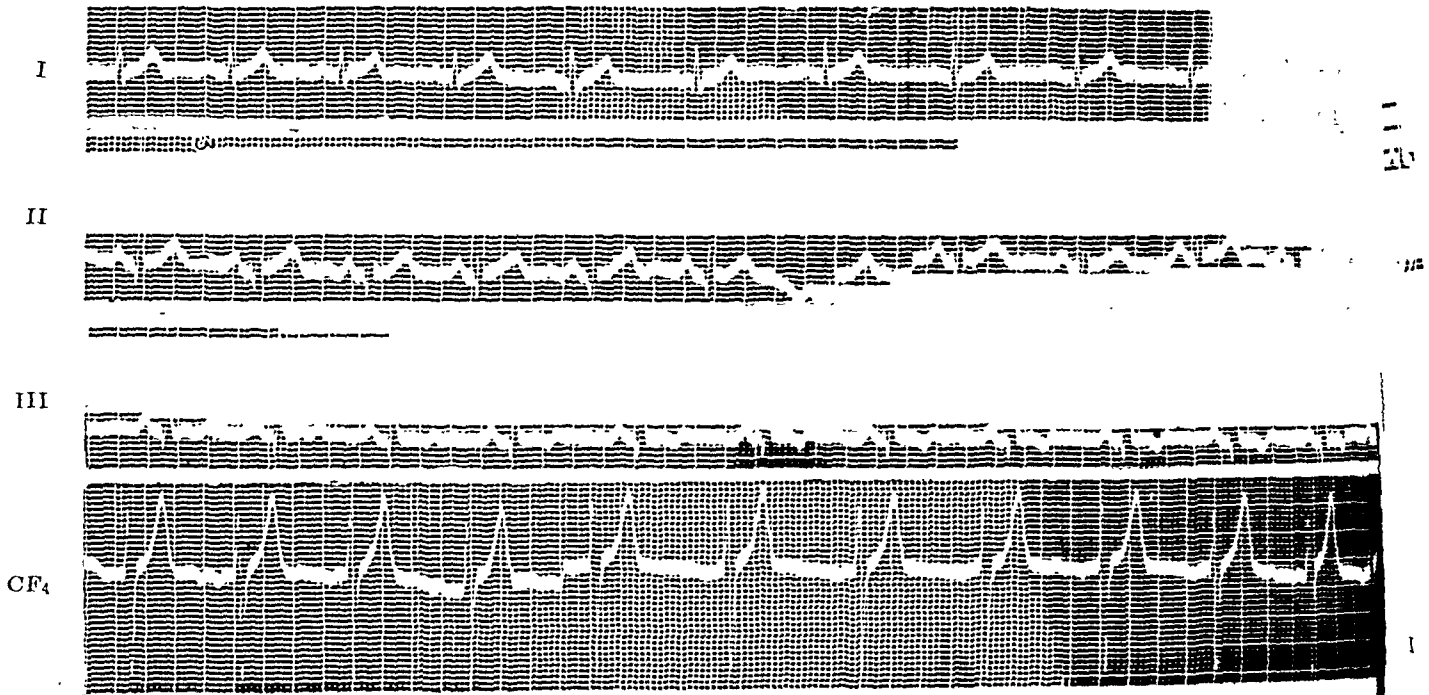


Fig. 6.—Maximal exhalation. No abnormal complexes were produced.

This tracing was then immediately repeated and the patient was to inhale maximally and to hold his breath while each lead was being taken (Fig. 5). Expected changes in amplitude of R and T waves are seen as well as reversal in the direction of T_3 . No effect on the duration of the P-R or QRS intervals is observed. However, it was demonstrated that conduction in the aberrant pathway could take place under this condition (arrow in Lead CF_4 of Fig. 5 points to abnormal complexes), but was not produced by deep inspiration as is seen in the resumption of normal complexes. Following this, another tracing was taken while the patient was exhaling maximally during each lead (Fig. 6). No abnormal complexes were produced. Finally, the patient was given the Master two-step exercise test. Immediately after this exercise, tracings were taken. Except for the sinus tachycardia, no changes were noticeable (Fig. 7). Eight minutes after the exercise test the tracings were repeated (Fig. 8). The sinus tachycardia had subsided, but a series of abnormal beats could now be seen in Lead CF_6 , indicating that exercise probably did not cause abnormal conduction in this patient.

COMMENT AND CONCLUSION

The case which has been presented shows clearly that the discovery of the existence of anomalous A-V excitation may require more than one routine electrocardiogram. The determination of this condition, even as a latent disturbance, may be important since Wilson,² Vakil,³ Nielsen and associates,⁴ Wood, Wolferth, and Geckeler,⁵ and Kimball and Burch⁶ have reported fatalities believed to be due to arrhythmias occurring in patients exhibiting anomalous A-V excitation.

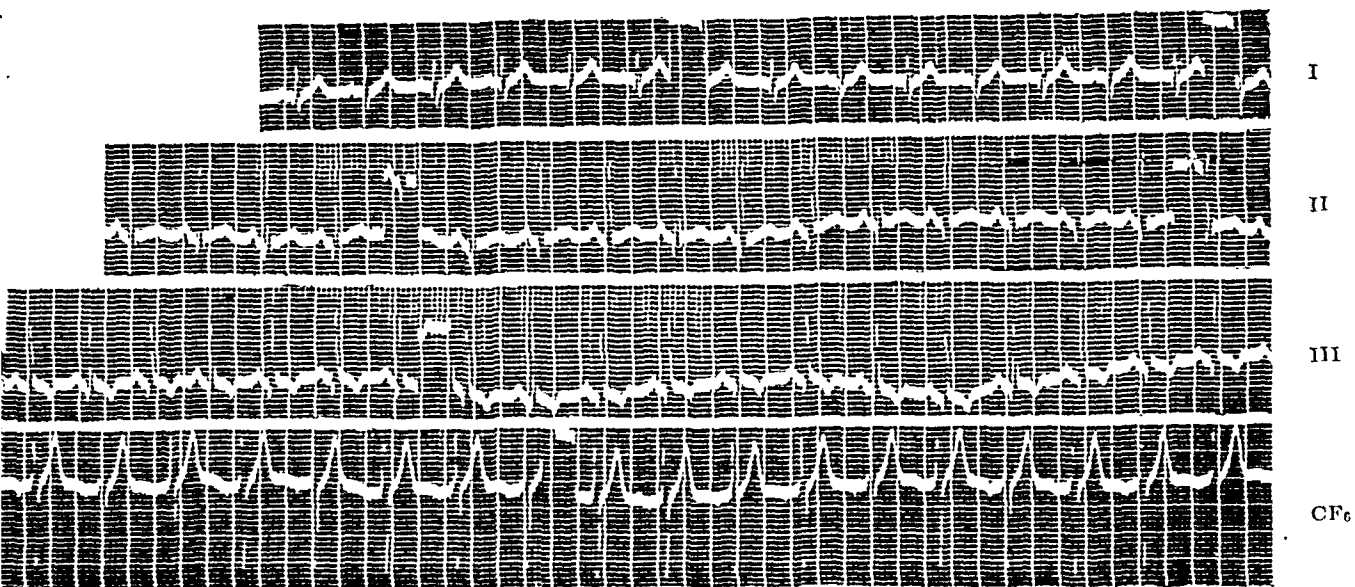


Fig. 7.—Immediately after exercise. No changes except for sinus tachycardia.

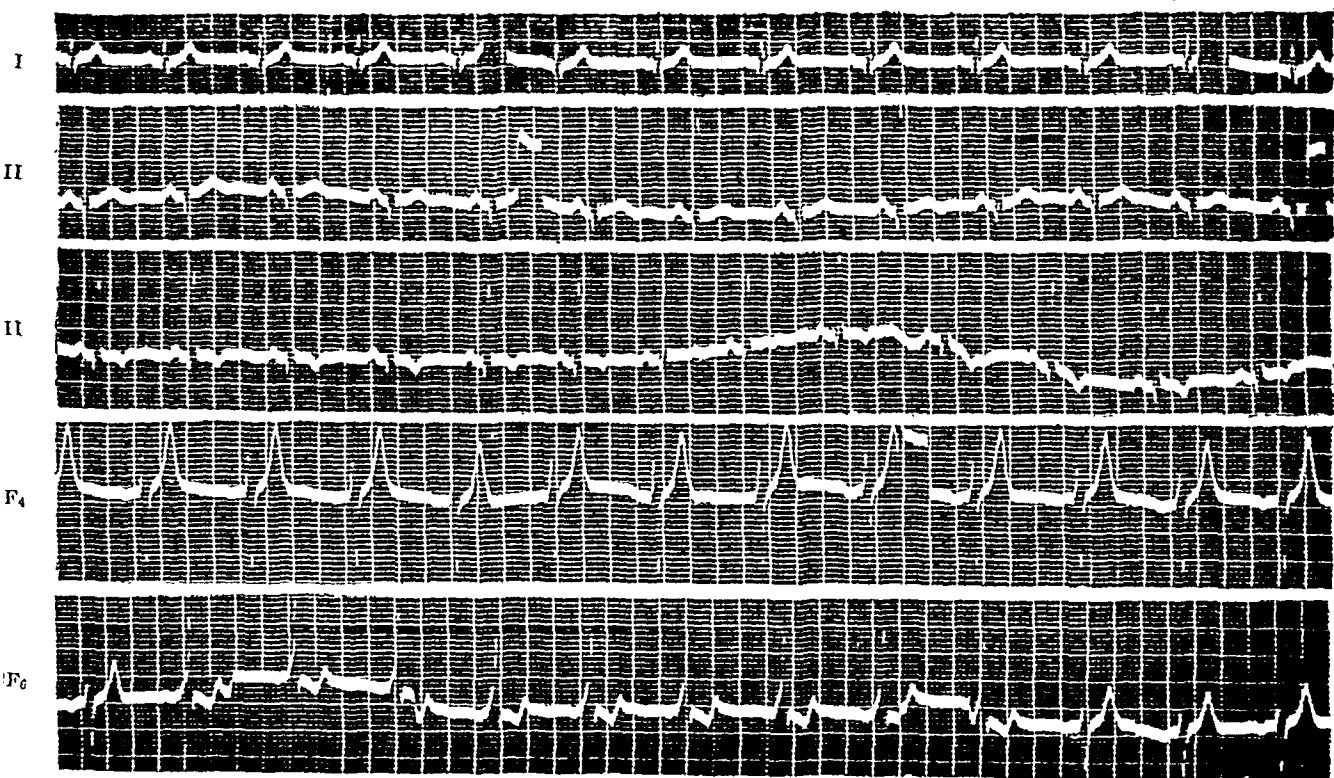


Fig. 8.—Eight minutes after exercise. A series of abnormal beats are now present in Lead CF₆.

REFERENCES

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5:685, 1930.
2. Wilson, F. N.: Recent Progress on Electrocardiography and the Interpretation of Border-line Electrocardiograms, *Proc. Life Insurance Med. Dir.* 24:96, 1938.
3. Vakil, R. J.: A Case of Mitral Stenosis With Apparent Bundle Branch Block, Short P-R Intervals and Attacks of Paroxysmal Tachycardia, *Indian M. Gaz.* 77:521, 1942.
4. Nielsen, A. L., Mortensen, V., and Eskildsen, P.: *Nord. med.* 21:450, 1943. (Quoted by Wood F. C., Wolferth, C. C., and Geckeler, G. D.⁵)
5. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, *AM. HEART J.* 25:4, 1943.
6. Kimball, J. L., and Burch, G.: The Prognosis of the Wolff-Parkinson-White Syndrome, *Ann. Int. Med.* 27:239, 1947.

ERRATUM

In the article by Bing et al. entitled "The Measurement of Coronary Blood Flow, Oxygen Consumption, and Efficiency of the Left Ventricle in Man," page 1, July, 1949 issue of the JOURNAL, in Fig. 8 some of the points obtained were mistakenly plotted against the cardiac indices. However, after correction of this error, some correlation between cardiac output and coronary flow is still present.

Abstracts and Reviews

Selected Abstracts

McClure, R. D., Behrmann, V. G., and Hartman, F. W.: *The Control of Anoxemia During Surgical Anesthesia With the Aid of the Oxyhemograph.* Ann. Surg. 128:685 (Oct.), 1948.

The authors emphasize the value of determining the oxygen saturation of the blood during surgical operations performed under various anesthetic agents. They trace the origin and development of the portable oxyhemograph and present data to prove the value of the instrument in the control of anoxemia during anesthesia. They point out the limitations of intermittent gas analyses because of the rapid fluctuations of oxygen saturation. The oxyhemograph makes tracings of the fluctuation of oxygen saturation of the blood with the respiratory cycle.

Several case reports are given where oxyhemography was used before, during, and following various surgical procedures under various anesthetic agents such as Pentothal, Pentothal-nitrous oxide-oxygen, cyclopropane, ethylene and ether, and Spinocain. The oxyhemograph demonstrated that patients under Pentothal showed considerable individual susceptibility. The method also showed the advantage of 100 per cent oxygen inhalations over room air prior to, during, and following the Pentothal, (2) the decreasing tolerance to Pentothal in prolonged procedures, and (3) the importance of using at least a 60 to 40 nitrous oxide to oxygen mixture as a supplement to Pentothal. Under cyclopropane, ethylene-ether, or Spinocain, patients did not show decreasing tolerance or cumulative effect, as determined by oxyhemography.

BECK.

Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E., and Blalock, A.: *The Surgical Treatment and the Physiopathology of Coarctation of the Aorta.* Ann. Surg. 128:803 (Oct.), 1948.

The authors report on twenty-three patients with coarctation of the thoracic aorta who have been operated upon. Thirteen of the patients were 20 years of age or above, while ten were younger. An anastomosis was completed in twenty-one of the twenty-two patients in whom it was attempted. In seventeen patients the stenosis was resected and an anastomosis of the proximal and distal ends of the aorta was performed. In four patients in whom the proximal segment of the aorta was too short for end-to-end suture, the left subclavian artery was used as a by-pass around the stenosis. There were three deaths in the series, including one in a child who had multiple congenital defects which had been recognized preoperatively.

Two observations were made during the three weeks' postoperative period. In every patient where headache was a prominent preoperative symptom, it became conspicuously absent postoperatively. Also, the systolic blood pressure in arm and leg required some five to ten days to stabilize.

The ideal operation is one in which the stenotic area is excised and the proximal and distal ends of the aorta are united by suture. The question has been raised as to whether one should employ the left subclavian artery to by-pass the point of stenosis if the ideal operation cannot be performed. It is the authors' contention that this method should be used provided one does not have to sacrifice the large intercostal collateral arteries which arise from the aorta just beyond the point of stenosis. In earlier operations, one or more pairs of intercostal arteries immediately distal to the point of coarctation were doubly ligated and divided. Now, the authors try to spare these arteries. A modified Potts arterial clamp is introduced in the free space between the points of

origin of the left common carotid and the left subclavian arteries. This clamp occludes the aorta completely, but permits some circulation through the subclavian artery. A single layer of sutures which includes the entire thickness of the wall of the aorta has been used in the twenty-three operations.

Physiologic investigations disclosed no significant deviation of the cardiac output from normal. Blood flow through the arm, which was elevated before operation, fell following surgery. The blood flow through the leg rose postoperatively. Hypertension in the upper part of the body and hypotension in the legs were observed preoperatively. After operation, these pressures tended to equalize. Analysis of the physiologic data indicated no generalized elevation of peripheral vascular resistance. It is probable, therefore, that the hypertension in coarctation of the aorta is not attributable to a renal pressor mechanism, but is due to the resistance of the stenosis and collateral arteries.

BECK.

Murray, G.; Closure of Defects in Cardiac Septa. Ann. Surg. 128:843 (Oct.), 1948.

The author discusses the high incidence of patent interventricular and interauricular septa which he found to be approximately 50 per cent in 350 congenitally diseased hearts which were examined. He carried out many studies in the experimental closure of septal defects and also studied the anatomic relations of the septa to various landmarks on the outside of the heart. Clinically, he carried out three operations on individuals with a patent interauricular septum and on one patient with a patent interventricular septum. Three of the four patients lived and were thought to be improved. Indications for operative intervention were enlargement of the heart, cyanosis, lack of energy, and evidence of inadequate cardiac function.

The method of closing the interventricular septum consisted of the passing of a living strip of fascia lata across the defect and allowing a thrombus to form on it. After a few days, heparin was utilized to prevent too great extension of the thrombus. The auricular septal defect was closed by means of sutures which pulled the anterior and posterior walls of the auricles together

LORD.

Beck, C. S.: Revascularization of the Heart. Ann. Surg. 128:854 (Oct.), 1948.

The author presents a third method for revascularization of the heart. This method consists of arterialization of the coronary sinus. Arterialization of the sinus was accomplished by grafting a systemic artery into the sinus and also by making a new branch from the aorta to the sinus using a free graft of artery or vein. Arterialization of the coronary sinus is effective physiologically. After anastomosis has been made it is possible to ligate a major coronary artery with little or no mortality and with little or no infarction. The author discusses the findings obtained by injection studies of dead specimens (dogs) and the various problems concerning circulation in the heart which invite further study.

One patient with severe coronary artery disease was operated upon. A free graft of a brachial artery was placed between the aorta and coronary sinus. A fresh infarct developed in the interventricular septum probably at the time of operation. The anastomosis was patent at the time of death one day later. The author believes that the time is near when the operation can be applied to patients.

BECK.

Roskam, J., Renard, C. H., and Swalue, L.: Inconstancy and Variability of the Vascular Fragility Test Even in Purpuric Conditions. Blood 3:1112 (Oct.), 1948.

It is pointed out that purpura and abnormal bleeding are due to hemic and vascular factors and that intradermal purpura is the result of multiple factors which are difficult to analyze. The importance of the fragility of vessels in the production of petechiae in purpuric patients has been stressed previously. A list of conditions in which this phenomenon has been observed is given.

The intensity of the purpura induced by venous stasis is approximated by the number of petechiae which occur during the test, but reference is made to the statement that there is a qualitative as well as a quantitative significance to the test, that is, that petechiae with a diameter over 1.0 mm. possess a significance similar to that of an increased bleeding time. These

large petechiae are observed in subjects with a hemorrhagic condition, and generally, the more severe the condition, the larger is the diameter of some of the petechiae.

The vascular fragility test which the authors used consisted of the application above the elbow of the cuff of a Boullitte oscillometer, inflated halfway between the maximal and minimal arterial pressure of the patient, for fifteen minutes. After decompression, the induced purpura on the whole surface of the forearm and hand was examined and recorded.

Two cases of purpura simplex are described, one with a strongly positive vascular fragility test and one in which it was completely negative. The latter case indicated the great variability of the vascular fragility test at different times in symmetrical areas of skin in a case of chronic hemorrhagic purpura. The response in these cases shows the complexity of the factors producing the purpuric eruption and it demonstrates the variability and inconstancy of the vascular fragility test.

BEIZER.

Jaques, L. B., and Ricker, A. G.: The Relationship Between Heparin and Clotting Time. Blood 3:197 (Oct.), 1948.

In a previous study it was shown that the clotting time depends upon both the coagulant power of the blood and the ability of the body to remove heparin from the circulation. The present study consists of further observations of the effect of heparin dosage on the clotting time in the dog.

When heparin was added to blood, *in vitro*, a linear relationship was found to exist between the heparin dosage and the logarithm of the clotting time. The slope of this curve was used to obtain the "heparin sensitivity value." No correlation was found between the normal clotting time and the sensitivity to heparin. The sensitivity of blood to the anticoagulant action of heparin depended upon the individual from whom the blood was taken, and upon the technique used both for removal of the blood and for determination of the clotting time. Important technical factors that caused variable results were noted, such as whether the vein has been exposed or merely punctured; moistening of the syringe with saline; removal of the needle before the blood has been transferred to the tube; and different surface coatings. Temperatures were important in that the activity of heparin increased at temperatures above and below the range of 20 to 25° centigrade. Despite these variables, it was felt that the clotting time was valuable in the control of heparin administration if the technical factors were properly controlled. It was suggested, however, that heparin should be administered on a weight or potency basis rather than on the basis of an arbitrary clotting time.

A ten- or fifteen-minute period was necessary in *in vivo* experiments for the clotting time to reach its peak unless very large doses were given. This would indicate that the delay was not due simply to the time required for mixing with the blood. From *in vitro* experiments it was evident that a certain period of time was required for heparin to combine with the components of the clotting system before it could exert its maximum anticoagulant effect. This also explained the observation that the clotting time *in vivo* was always three to ten times greater than that obtained *in vitro*. No evidence of a biphasic response to heparin was found. The interval required for the clotting time to return to normal was quite short and, with a given dose, was constant with different animals.

A test was described which showed the response of the individual to heparin added to the blood both *in vitro* and *in vivo*. This, in effect, combined the Waugh and Ruddick tests, which indicates the coagulability of the blood by an *in vitro* test, and the De Takats test, which is essentially a heparin tolerance curve. This curve is determined by the coagulability of the blood itself and also by those processes whereby the heparin activity disappears from the circulation.

The authors conducted the combined heparin sensitivity test as follows: 0.0, 0.2, 0.5, and 1.0 unit of heparin in 0.3 c.c. of saline was placed in tubes in the coagulometer. Five cubic centimeters of blood were drawn and 1.0 c.c. added to each tube. The first and last portions of blood were discarded. The clotting times of the samples were determined to establish the *in vitro* curve. Thirty units per kilogram of heparin were then injected intravenously and the clotting time determined at five- to ten-minute intervals. This was usually repeated with a dose of 100 units per kilogram to give two *in vivo* curves. The results were plotted on semi-

logarithmic paper to give linear results. The response in vitro measures the sensitivity of the clotting mechanism to heparin, while the in vivo response, when interpreted in the light of the in vitro response, measures the ability of the body to remove heparin from the circulation.

In experiments carried out by this method, the coagulability of the blood was found to be decreased in dogs anesthetized with pentobarbital, variable with ether, and unchanged with urethane. Hypercoagulability resulted from the injection of India ink or evisceration. Nephrectomy has little effect. Pentobarbital and nephrectomy had no effect on the sensitivity of the blood to the anticoagulant effect of heparin, while ether anesthesia caused an increase in sensitivity. Urethane caused a decrease, but the injection of India ink or evisceration caused a marked decrease in sensitivity. None of these procedures affected the duration of heparin action in the body.

BEIZER.

DeGraff, A. C., Batterman, R. C., and Rose, O. A.: Digitoxin: Its Evaluation for Initial Digitalization of the Patient With Congestive Heart Failure. J. A. M. A. 138:475 (Oct. 16), 1948.

The authors present an evaluation and comparison of three methods of oral digitalization with digitoxin. The study was made on groups of hospitalized patients with varying degrees of chronic congestive heart failure. With few exceptions, the patients had never previously received any digitalis preparation; in no case had any patient received any digitalis preparation more recently than three weeks previously. Prior to digitalization the patients were observed for at least several days, during which control period no mercurial diuretics were administered. An attempt was made to determine both the therapeutic dose and the toxic dose of digitoxin in each case.

One group of patients was given digitoxin according to a multiple dose schedule consisting of an initial large dose followed by smaller doses at six-hour intervals. The initial dose varied from 0.4 to 1.6 mg., most patients receiving 0.6 mg., and subsequent doses varied between 0.2 and 0.4 mg., with the greatest number of patients receiving 0.3 milligram. The therapeutic dose, as determined by the occurrence of a definite sustained therapeutic effect, was ascertained in twenty-seven of the patients and ranged from 0.9 to 4.8 mg. (average, 2.2 mg.). Initiation of improvement occurred in most patients within twenty-four hours, but a satisfactory effect was not achieved until at least forty-eight hours. The toxic dose varied from 1.5 to 9.3 mg. (average, 4.1 mg.). The best dosage scheme was found to be 0.6 mg. initially, followed by 0.3 mg. every six hours until the desired therapeutic effect was obtained.

In a second group of patients, none of whom was acutely ill, daily single doses of 0.4 mg. of digitoxin were given. Digitalization was achieved in nine of the twelve patients, the desired therapeutic response occurring in from three to six days with a total dosage varying between 0.9 and 2.4 mg. (average, 1.7 mg.). The toxic dose, as determined in eleven cases, ranged from 1.6 to 8.0 mg. (average, 3.8 mg.).

In order to determine the efficacy of the single-dose method of digitalization, as advocated by Gold, eighteen patients with chronic auricular fibrillation in varying degrees of congestive failure were given single doses of 1.2 mg. of digitoxin, as recommended by Gold, and were observed during the ensuing twenty-four hours for signs of clinical improvement. Adequate digitalization occurred in only three patients, including two who had been in only mild failure. Seven of the group evinced no clinical effects from the single "digitalizing" dose of the drug, and the remaining eight patients displayed slight but inadequate improvement. In those patients who were not adequately digitalized after twenty-four hours, additional doses of digitoxin were given at intervals of six hours until satisfactory response resulted. Eleven patients required 0.4 to 3.3 mg. (average, 1.6 mg.) more of the drug than the initial 1.2 mg. dose to achieve a good therapeutic effect. The toxic dose was found to vary between 2.1 and 7.1 mg. (average, 4.6 mg.).

The authors point out that although the toxic manifestations of digitoxin are in no way different from those resulting from the whole leaf of *Digitalis purpurea*, digitoxin toxicity persisted strikingly longer, lasting for many days in several patients, although the milder toxic symptoms usually subsided in from two to three days. The persistence of the toxic manifestations was the result of the slow dissipation of digitoxin.

Of the three methods of oral administration which were investigated, the multiple-dose method was deemed the one of choice. It was stressed, however, that the "average" dose is only a rough guide and that a total dose optimum for the individual patient must be administered before a satisfactory therapeutic response is attained.

It is the opinion of the authors that digitoxin offers no particular advantage over digitalis leaf and that because of the possibility of severe and prolonged toxicity, digitoxin is not the glycoside of choice.

HANNO.

Kessler, D. L., and Hines, L. E.: Hazards of Thiocyanate Therapy in Hypertension. J. A. M. A. 138:549 (Oct. 23), 1948.

The authors review the toxic effects of thiocyanate administration and present reports of three cases, one of which terminated in death, illustrating the hazards of thiocyanate therapy for essential hypertension.

In the first case, treatment with thiocyanates had been ineffective in producing a fall in blood pressure both before and after lumbodorsal sympathectomy. After thirteen months of thiocyanate therapy the patient developed weakness, dizziness, vomiting, confusion, and disorientation. The serum thiocyanate level at this time was 8.8 mg. per cent, a concentration below that at which toxic manifestations ordinarily occur. Eighteen days after discontinuation of the drug, the blood level had fallen to 5.5 mg. per cent and complete recovery had taken place.

A second hypertensive patient was placed on 0.3 Gm. of potassium thiocyanate three times daily. The blood concentration two weeks later was 8 mg. per cent. One week later, while he was on the same dosage of the drug, weakness, palpitation, slurred speech, mild disorientation, and soreness of the lips, tongue, and mouth developed. The serum thiocyanate level was found to be 22 mg. per cent, a concentration higher than the desired therapeutic range of from 8 to 12 mg. per cent. Recovery took place eight days after thiocyanate therapy was stopped, the blood level falling to 10 mg. per cent.

A third patient with severe renal damage who had been taking 0.26 Gm. of potassium thiocyanate three times daily for a period of one month developed a severe exfoliative dermatitis and hepatic necrosis which terminated fatally. The blood thiocyanate level in this patient was 25.3 mg. per cent.

The authors caution that the margin of safety between therapeutic and toxic levels is narrow in some patients, and they point out that moderate toxic symptoms are not uncommon even when blood levels are within a range recommended as safe.

HANNO.

Melville, K. I.: Further Studies on the Antifibrillatory Action of Coronary Dilator Drugs. J. Pharmacol. & Exper. Therap. 94:136 (Oct.), 1948.

The author, using intact, pentobarbital-anesthetized dogs, tested ephedrine, amyl nitrite, sodium nitrite, and nitroglycerine for their antifibrillatory effects by evaluating their efficacy in preventing chloroform-epinephrine induced fibrillation.

All four of the drugs studied prevented premature contractions and fibrillation when given in suitable dosage. Amyl nitrite, sodium nitrite, and nitroglycerine prevented fibrillation despite a marked increase in arterial blood pressure when epinephrine was administered during chloroform inhalation. Larger amounts of the nitrite group abolished the epinephrine pressor effects as well as the fibrillatory effects. Ephedrine protected the heart against fibrillation despite a marked pressor response, and despite premature contractions produced by ephedrine prior to epinephrine administration, which, in turn, produced a further rise in arterial pressure.

Fibrillation, caused by epinephrine during chloroform administration, is commonly ascribed to the pressor effect of the epinephrine. This work would indicate that another mechanism must be responsible for the fibrillation. The antifibrillatory action of the four drugs used in this work, as well as that of both papaverine and atabrine, is ascribed by the author to their common property of acting as coronary dilators.

GODFREY.

Kergin, F. G., Bean, D. M., and Paul, W.: Anoxia During Intrathoracic Operations (A Preliminary Report). J. Thoracic Surg. 17:709 (Oct.), 1948.

Little information is available in regard to the degree and duration of anoxia which is likely to be harmful. Investigations carried out in aviation medicine have been done on fit individuals who were not undergoing a surgical operation, and these have shown great individual variation in tolerance for anoxia. The method used in this investigation was to record continuously the level of arterial oxygen unsaturation during and immediately after major thoracic operations by means of an oximeter, which, by means of color filters and a two-channel photocell, gives a continuous recording of the oxygen unsaturation in the blood of the fully dilated capillaries of the ear.

Observations have been made in seventy intrathoracic operations. Pneumonectomies, lobectomies, and esophagectomies were done under intratracheal ether-oxygen anesthesia. Thoracoplasties were done under intratracheal cyclopropane. In none of the thoracoplasty cases was there any significant fall in oxygen saturation. However, in the cases where the pleural space was opened, the oxygen saturation was subject to surprising swings. It was not unusual to encounter an abrupt fall to 25 to 30 per cent oxygen unsaturation followed by a rise when positive pressure was applied. In addition, as the operation progressed, there was a gradually increasing oxygen unsaturation in many patients. This latter can be prevented or corrected by the application of positive pressure anesthesia at a pressure of 15 mm. of mercury.

From this investigation, to date, it is concluded that with this method of anesthesia a significant degree of anoxic anoxia may occur during major intrathoracic operations. This is probably due to a progressive atelectasis of the contralateral lung, and it can be prevented or corrected by the use of positive pressure anesthesia. Since anoxia during operation cannot be recognized by clinical signs, the use of the oximeter is a valuable addition to the technique of major intrathoracic operations.

BECK.

Douglass, R.: Anomalous Pulmonary Vessels. J. Thoracic Surg. 17:712 (Oct.), 1948.

The surgical importance of anomalous pulmonary vessels is apparent. The author tabulates reports relating to anomalous pulmonary arteries and veins in the anatomic and pathologic literature. Four cases encountered during operation are reported in addition to ten cases previously reported by surgeons. Two types of anomalous pulmonary arteries are reported by both pathologists and surgeons, the more common type arising from the aorta below the hilum, the second arising from the abdominal aorta or celiac axis. In the pathologist's material, anomalies are approximately equally distributed between the right and left sides. In the surgical cases, the vessel was on the left side in ten, on the right side in one, and the side was not specified in three. The associated pulmonary pathology was an infected cyst in eight instances, a fact which suggests that multiple congenital anomalies were present.

BECK.

Blood, D. W., and Patterson, M. C.: Effect of Aminophyllin on the Coagulation of Human Blood. Proc. Soc. Exper. Biol. & Med. 69:130 (Oct.), 1948.

Aminophyllin, 0.48 Gm., was given intravenously over a ten-minute period to eighteen patients. In none of them was there any evidence of liver disease or disorder of the blood-forming organs and in no case were drugs being taken which are known to affect the clotting of the blood. Determinations of the clotting and prothrombin times were done before injection and thirty minutes and one hour after the injection. A second group of twelve patients were given 0.2 Gm. of aminophyllin by mouth four times a day for seven days. Determinations of clotting and prothrombin times were done both before and following the period of administration of the drug. The clotting time was determined by a modification of the Lee-White method. The prothrombin time was determined by a slight alteration in the Link-Shapiro modification of Quick's method. An identical test was also done using 12.5 per cent plasma. The strength of the thromboplastin used was found to vary considerably with different lots of the preparation, and for this reason a control plasma prothrombin time was determined on a normal subject at the time each patient was tested. Prothrombin times were all expressed as percentage of the normal control for a given day. Duplicate determinations were done on all tests.

The authors found that following the administration of aminophyllin by either the oral or intravenous route there were no statistically significant changes in the clotting time of the blood, or in the prothrombin time of undiluted or diluted (12.5 per cent) plasma.

KLINE.

Wilson, A., and Stoner, H. B.: The Effect of the Injection of Acetylcholine Into the Brachial Artery of Normal Subjects and Patients With Myasthenia Gravis. Quart. J. Med. 16:237 (Oct.), 1947.

The responses to nicotine and muscarine were studied in thirteen normal subjects and in twelve patients with myasthenia gravis, not under the influence of prostigmine, after intrabrachial injection of 10 to 80 mg. of acetylcholine.

The nicotine effects, flexion, loss of muscle power, and fasciculation, seen in the normal subjects and in the patients with myasthenia gravis after the injection of acetylcholine were recorded. The results show that a flexion response occurred in an almost equal number of cases in each group. The flexion response was confined to the fingers and, although involuntary, could usually be controlled by the patient, who was able to extend the fingers and counteract the contraction. Where the contraction occurred in patients with myasthenia gravis it did not differ from that seen in the normal subjects. Signs of excess acetylcholine did not occur in every normal subject, but the loss of power in the hand was more frequent in that group. The paresis was partial and persisted for from one to three minutes. In a number of cases the flexion response was followed by loss of power in the hand grip. This suggests that a concentration of acetylcholine sufficient to produce stimulation was followed by a greater concentration with resultant depression.

The muscarine effects, vasodilatation and sweating, were also studied. The onset of the flush usually occurred within two to five seconds and spread from the forearm to the wrists and fingers. Where this vasodilatation of the fingers was observed, it was usually, but not always, associated with sweating of the palmar surface of the hand. The flush disappeared gradually and in some cases had completely disappeared after six minutes; in other subjects, however, it was still present after twenty minutes. The time of appearance and duration of sweating was as varied as was the vasodilatation, and no correlation was observed between the flush and sweating. The muscarine responses varied from case to case. This variability is discussed in relation to the reliability of this method of testing the sensitivity of muscle to injected acetylcholine in man.

No evidence of a striking difference in the sensitivity of normal and of myasthenic muscle to nicotine injected intra-arterially was observed; nor was it demonstrated that myasthenic muscle is peculiarly hypersensitive to acetylcholine.

BELLET.

Effersøe, P.: Nephrectomy in Hypertension and Unilateral Renal Disorder. Acta med. Scandinav. 131:10 (No. 1), 1948.

The author reports two cases of hypertension and unilateral renal disease in which nephrectomy has been performed. Case 1 is that of a 39-year-old man whose nonfunctioning left kidney, the seat of pyonephrosis, was removed because of hypertensive encephalopathy. After nephrectomy there was marked symptomatic and eye-ground improvement and a blood pressure fall from preoperative levels of 200-180/130-100 to 120/70. At the end of fifteen months, symptoms suggesting hypertensive encephalopathy had returned, and the blood pressure on readmission to the hospital was 170/115, though it fell to 140/90 with rest in bed. The second patient was a 53-year-old woman who had a left nephrectomy on surgical grounds for chronic pyelonephritis and nephrolithiasis. Her blood pressure of 200-190/120-110 showed only a transient postoperative decline.

SAYEN.

Lohman, A. J. M.: Mediastinitis Anterior Chronica. Acta med. Scandinav. 131:51 (No. 1), 1948.

The author is of the opinion that certain acute tracheobronchial or pharyngeal infections produce mediastinitis by extension to the peribronchial and peritracheal lymph glands. A pericarditis follows which may or may not cause an exudative reaction in the pericardial cavity itself. Following the acute phase in which symptoms may be minimal or absent, a chronic anterior mediastinitis may occur. Five such cases are reported.

The characteristic history was of an acute influenza-like illness associated with persistent substernal oppression over periods varying from four weeks to seven years, most marked with exertion or deep respiration. Lateral roentgenograms revealed indrawing of the xiphoid process, an obtuse angle between the diaphragm and the anterior chest wall, a thickening of the soft tissues of the lower precordium, and an unusually perpendicular direction of the long axis of the heart shadow.

The electrocardiogram was normal, except in one patient thought to have associated coronary disease. The tuberculin reaction was negative in three instances and strongly positive in the one patient whose diagnosis was confirmed by operation. This patient was found to have an anterior *mediastinum filled with tough connective tissue 1.5 cm. thick*. The xiphoid, which was dislocated backward, was excised with the lowermost third of the sternum. There was increased pericardial fluid but no adhesions. On section, edematous fibrous tissue with slight polymorphonuclear and lymphocytic infiltration was found. The patient lost his symptoms for the duration of the two-year postoperative follow-up period.

The importance of considering chronic anterior mediastinitis in patients with precordial or substernal oppression that might otherwise be attributed to neurosis is stressed. Operative excision of the scar and the adherent xiphoid is believed indicated only for severe symptoms.

SAYEN.

Mortensen, V., and Warburg, E.: Chronic Constrictive Pericarditis. Acta med. Scandinav. 131:203 (No. 3), 1948.

The author reviews the literature and reports twenty-five cases of chronic constrictive pericarditis in which the diagnosis was confirmed by operation in nineteen, by x-ray in four, and by necropsy in one. The etiology was undetermined in two-thirds of the group; in three patients it was clearly tuberculous and in two, post-traumatic. Although symptoms suggesting rheumatic fever were present in 10 per cent, this incidence was not thought to be significantly greater than would be found among other groups of patients in a medical clinic.

Systolic blood pressures tended to be low, but pulse pressures were not always small and only once in nine instances was pulsus paradoxus demonstrated. T-wave abnormalities were present in most electrocardiograms and auricular fibrillation in a minority. Roentgenkymograms showed small cardiac pulsations regularly. Seventy-two per cent of heart shadows were normal in size. Forty-eight per cent showed calcification, which in general tended to be associated with enlargement and auricular fibrillation.

Pericardial resections were done on twenty patients. Nine died within a few days or weeks of the procedure. Four were unimproved, two dying, respectively, four and six years later. The results in seven were excellent. Five of the seven patients with calcification died and the other two were unimproved following operation. Two of the tuberculous patients died and one was rendered symptom free. Of the five patients not operated on, three died within 3 to 6 years of diagnosis, while two were still alive, respectively, seven and thirteen years later.

The authors feel that older persons should not be operated on, but that younger individuals should be explored and pericardiectomy done if calcification is not conspicuous; otherwise the risks have proved great and the results poor.

SAYEN.

Barnes, D. W. H., Loutit, J. F., and Reeve, E. B.: A Comparison of Estimates of Circulating Red Blood Cell Volume Given by the Ashby Marked Red Cell Method and the T 1824 Haematocrit Method in Man. Clin. Sc. 7:135, 1948.

The authors measured total red cell volume by use of the Evans blue-dye and the Ashby methods.

It was found that about 5 per cent of the packed red cell volume consists of trapped plasma, and hematocrit readings should be appropriately corrected. In twelve patients and eight normal subjects, simultaneous estimations were made by both methods. On the average, the red cell volume calculated by the plasma dye and hematocrit method was 13 per cent greater than by the Ashby method. From other similar reported series, it appears that the dye and carbon monoxide methods give approximately a 15 per cent greater estimate than the Ashby and radioactive isotope labeled methods.

It is concluded that the dye method overestimates the "true volume." The true red blood cell volume equals the red cell volume determined by the dye method times the factor $0.87 \pm .06$.
WAIFE.

Gordin, R.: Alternating Nodal and Sinus Rhythm in a Case of Situs Viscerum Inversus. *Acta med. Scandinav.* 131:422 (No. 5), 1948.

The author presents the case of an 83-year-old woman with situs inversus and extensive myocardial scarring who manifested A-V nodal rhythm alternating under conditions of exertion or excitement with sinus rhythm at a faster rate. Sinus rhythm could be produced briefly by carotid sinus pressure (thought to be on the basis of pain rather than vagal stimulation) and by atropine.
SÄYEN.

Barnes, D. W. H., Loutit, J. F., and Reeve, E. B.: Observations on the Estimate of the Circulating Red Blood Cell Volume in Man Given By T 1824 and the Haematocrit, With Special Reference to Uncorrected Dye Loss From the Circulation. *Clin. Sc.* 7:155, 1948.

The discrepancy between the T-1824 estimate of red cell volume and the Ashby (labelled red cell) and radioactive red cell methods could be due either to uncorrected loss of dye from the circulation or to unequal distribution of red cell and plasma in the circulating blood.

These investigators found that it takes about thirty or forty seconds for dye added to plasma to become bound to plasma albumin and no great loss of unbound dye can be expected to occur. Comparison of changes in concentration of marked red cells and T-1824 in the few minutes following transfusions suggested that the "mixing phase" of the dye dilution curve is actually due to mixing. Errors due to impurities in the injected dye solution and possible errors due to dye loss ignored by the extrapolation method are probably very small.

It seems, therefore, that the overestimation of red cell volume given by the dye-hematocrit method is due to the unequal distribution of plasma and red cells in the circulating blood.
WAIFE.

Van Wyk, J. J., and Hoffmann, C. R.: Periarthritis Nodosa. *Arch. Int. Med.* 81:605 (May), 1948.

A case is described of a 71-year-old Negro woman in whom a fatal exfoliative dermatitis developed as a result of medication with diphenylhydantoin sodium ("Dilantin sodium"), which was continued in the face of clear evidence of hypersensitivity to the drug. At autopsy, inflammatory, necrotizing arterial lesions of the type occurring in serum sickness and in hypersensitive reactions to the sulfonamide drugs and to iodine were present in the liver, spleen, kidneys, bone marrow, and skin. These lesions are a manifestation of the anaphylactic type of hypersensitivity and the authors suggest that continued medication with diphenylhydantoin sodium (as well as as phenobarbital, iodine, sulfonamide drugs, and phenylethylhydantoin "Nirvanol") after the clinical evidences of hypersensitivity have developed may lead to periarthritis nodosa.
BERNSTEIN.

Hultgren, H. N.: Calcific Disease of the Aortic Valve. *Arch. Path.* 45:694 (June), 1948.

The author examined one hundred adult hearts from consecutive autopsies. The ages of the patients ranged from 26 to 86 years, the average age being 58 years; one-third of the number from female patients. In addition to routine gross inspection, he employed a roentgen visualization of the dissected aortic valves in an effort to analyze more objectively the grade of calcific deposit and to identify the earliest essentially microscopic lesions.

Of these one hundred hearts, forty-six had demonstrable calcific deposits in the aortic valves; eleven were immediately withdrawn from analysis because of the presence of undoubted rheumatic disease, and one because of bicuspid deformity with calcification. The average age of the remaining thirty-four hearts was 67 years, in contrast to the over-all average of fifty-eight. In addition to this demonstrable increase in calcification parallel with increasing age, it was noted that the aortic valvular calcification roughly paralleled the degree of aortic calcification, with particular reference to the lumbar aorta.

The following was also recorded: In this nonrheumatic group aortic valvular calcification was not encountered under the age of 40 years; and while there was no sexual predominance from the standpoint of actual incidence of aortic valvular calcification, it was yet apparent that massive calcification of aortic valves predominantly affected the male sex. Significantly in this type of nonrheumatic calcific aortic valvular disease, only minimal (lateral) adhesion of valve cusps was found, and there was no rolling or thickening of the free edge of the leaflets, even with severe calcification.

The histologic examination revealed that calcification made its earliest appearance inside the sinus of Valsalva at the base of the leaflet, filling in the angle of insertion between the leaflet and the aortic wall. The fibrocollagenous tissue that normally exists in closely packed bundles in this area became frayed, acellular, and then pock-marked with small points of calcium deposit. Inflammatory reaction was slight and seemed to be intimately associated only with the presence of calcific deposit, since in other fields without the calcium, the acellular areas showed little or no such infiltration. In conjunction with the increased acellularity of the fibrocollagenous tissue in this area of valvular insertion, there was a deposit of lipoid material. The author emphasizes the absence of this lipid deposit on the ventricular aspect of the valve leaflets.

It is the author's opinion that fullblown aortic stenosis is a result of a process not necessarily associated with inflammatory heart disease. Signs of an inflammatory reaction, recent or old, are not recognizable in most of these cases. He therefore believes that calcification of the aortic valve, at least in many cases, is the result of a purely degenerative process without a rheumatic origin.

GOULEY.

White, N. K., and Edwards, J. E.: Anomalies of the Coronary Arteries. Arch. Path. 45:766 (June), 1948.

In the course of study of the coronary arteries in 600 hearts, four were discovered which showed an anomaly of those vessels. One heart from a 39-year-old man showed the unusual abnormality of a single coronary artery. One case showed both arteries arising in the left aortic sinus (ectopic origin of the right coronary artery). Two cases revealed the left circumflex artery arising from the right coronary artery.

Of interest is the fact that aside from one case, the hearts presenting these major anomalies of the coronary arteries were from elderly people, and of the group, only one of these patients died as a result of cardiac failure (a patient 81 years of age).

Even in the rare instances where a single coronary artery is presented, the theoretical risk of a totally ischemic heart following coronary disease is not definitely established. The remaining anomalies appear to have no important bearing on longevity.

GOULEY.

Soulie, P., Michel, J., and Baygin, R.: High Precordial Leads in Normal Subjects and in Patients With Coronary Artery Disease. Arch. d. mal du coeur 41:289 (July), 1948.

The authors investigated the value of a number of precordial positions located one and two intercostal spaces higher than those used for conventional leads. As previous observations by others have amply demonstrated, these leads, except for minor details, resembled the precordial electrocardiogram obtained from standard position in twenty-two normal individuals. In nine examples of myocardial infarction in various locations, these high leads confirmed the findings of the standard precordial positions and suggested to the authors upward extension of the lesion. No examples of high lateral infarctions were observed, and the difference between high lateral and standard precordial leads in vertically placed hearts was not emphasized.

HECHT.

Meyer, P., and Herr, R.: The Electrical Axis of Standard and Thoracic Leads Obtained by Means of an Artificial Dipole. Arch. d. mal. du coeur 41:325 (July), 1948.

Two stimulating electrodes designed to deliver approximately two volts were inserted into the chest of a cadaver. The position of the stimulating electrodes was varied with respect to the horizontal. This bipolar stimulator was placed in the center of, or to the right and to the left of, the sternum. The current was picked up by extremity electrodes.

Agreement between the calculated angle α from the limb lead records and the actual values was close if the dipole was located in the midline. With the dipole to the left of the sternum, clockwise deviation from the expected value up to 16° was obtained; with the dipole shifted to the right, deviations were between 7° and 37° in a counterclockwise direction. Unless these displacements were excessively large, the calculated and obtained values agreed within a small range. When the poles of the stimulating electrodes were inserted at various depths, the calculated angle α underwent slight variations but the differences between the actual and recorded values remained relatively insignificant.

The authors present their results as a further contribution on the validity of the Einthoven's triangle concept. HECHT.

Edwards, J. E., Christensen, N. A., Clagett, O. T., and McDonald, J. R.: Pathological Considerations in Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 23:324 (July 21), 1948.

In the infantile type, the coarctation of the aorta usually lies between a patent ductus arteriosus and the left subclavian artery. The adult type shows a zone of narrowing usually at the level of the aortic insertion of a closed ductus or immediately distal to it. Aberrations from these conditions are not infrequent.

When the ductus remains open, the intrapulmonary arteries and arterioles show significant morphologic changes. The region of the termination of the ligamentum arteriosum and the zone of aortic narrowing are described both as to gross and microscopic appearances. A striking finding is the "jet lesion" in the aorta distal to the stricture. This lesion is a localized corrugated patch of fibrous intimal thickening, which is considered to result from trauma by a jet of blood striking the wall after passing through the narrowed lumen. This defective area may interfere with surgical treatment and prevent favorable results.

These investigators have also observed that the area of narrowing is chiefly due to a sphincteric curtain of thickening of the aortic media which is present at all ages. In adolescents and adults, an additional layer of intimal thickening suggests progressive changes due to the trauma of eddy currents of blood at the point of stricture. The authors refute the Skodiak hypothesis for coarctation by overgrowth of the ligamentum arteriosum.

Concomitants of coarctation of the aorta are myocardial hypertrophy, bicuspid aortic valve, with aortic insufficiency, bacterial endocarditis, rupture of the aorta with dissection, and so-called congenital intracranial aneurysms of the circle of Willis.

ARKLESS.

Pugh, D. G.: The Value of Roentgen Diagnosis in Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 23:343 (July 21), 1948.

The pathognomonic roentgenologic sign in coarctation of the aorta is notching of the ribs. This is due to enlargement of the intercostal arteries which produces erosion of the superior aspect of the costal groove on the inner surface of the rib. This concept corrects the common statement in the literature that the notching is on the inferior aspect of the ribs. Similar notching occurs in intercostal neurofibromatosis and following intercostal artery enlargement due to vascular lesions of the thoracic wall. Minimal notching may be overlooked. No notching is present when the development of collateral circulation has been insufficient to cause enlargement of the intercostal arteries.

Other roentgenologic manifestations of coarctation of the aorta, such as lack of prominence of the aortic knob and left ventricular hypertrophy, are not of much diagnostic aid, but any and all roentgenologic criteria may help the surgeon decide on operability.

To evaluate the accuracy of roentgenologic diagnosis in this condition, ninety cases were studied. The author concluded that the clinical diagnosis of coarctation of the aorta is more accurate than the x-ray diagnosis. About a fourth of the patients did not exhibit the pathognomonic notching of ribs. The youngest patient in this group to show this sign was 8 years of age.

ARKLESS.

Wakim, K. G., Slaughter, O., and Clagett, O. T.: Studies on the Blood Flow in the Extremities in Cases of Coarctation of the Aorta: Determinations Before and After Excision of the Coarctate Region. Proc. Staff Meet., Mayo Clin. 23:347 (July 21), 1948.

These authors studied the resting blood flow in all extremities of fourteen patients with coarctation of the aorta by means of the venous occlusion plethysmograph with the compensating spirometer recorder. They compared these findings with the flow in corresponding extremities of fourteen normal persons under identical controlled conditions. Differences in blood flow were considered insignificant.

Nine of the patients with coarctation of the aorta were restudied following excision of the coarctate portion and anastomosis of the aorta. There was a slight average decrease of blood flow to the arms and a slight average increase of flow to the legs after the operation.

ARKLESS.

Brown, G. E., Clagett, O. T., Burchell, H. B., and Wood, E. H.: Preoperative and Postoperative Studies of Intraradial and Intrafemoral Pressures in Patients With Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 23:352 (July 21), 1948.

By the use of hypodermic strain-gauge manometers, intra-arterial blood pressure and pulse wave characteristics were studied in twenty-five patients with coarctation of the aorta and in six normal subjects. In the former group (1) systolic and diastolic pressures in the radial artery were elevated above the range of values observed for normal subjects, (2) systolic pressure in the femoral artery was reduced or within the range of values obtained for normal subjects while diastolic pressure was usually elevated above the normal range, (3) the ratios of femoral to radial systolic pressure and of femoral to radial pulse pressure were below the range of similar ratios obtained for normal subjects, (4) the onset of the femoral pulse wave was nearly always delayed beyond the onset of the radial pulse wave, and (5) the interval of time elapsing between the onset and the attainment of the peak in the femoral pulse was, with one exception, beyond the range of values observed in the normal subjects.

Similar studies were made on patients before and after corrective surgical procedures. One group included three individuals in whom anastomosis of the left subclavian artery and the thoracic aorta was accomplished after resection of the stenosed portion of the aorta. A second group comprised eight patients in whom the stenotic segment was resected and then anastomosis of the proximal and distal ends of the aorta accomplished. In the first group, the delayed onset of the femoral pulse wave usually seen in untreated individuals was eliminated postoperatively, but values for arterial blood pressure were similar in both groups. In the group in which end-to-end anastomosis of the aorta could be accomplished, much more striking changes in the cardiovascular dynamics toward the normal were observed.

ARKLESS.

Clagett, O. T.: The Surgical Treatment of Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 23:359 (July 21), 1948.

The author reports on the surgical experience in coarctation of the aorta at the Mayo Clinic. Twenty-one patients, fourteen male and seven female subjects, came to operation. The author suggests that the optimum age range for operation is 10 to 20 years. Before the age of 10 years the aorta is too small and there is a question as to whether the anastomosed segments will keep pace with the normal growth of the body. After the age of 20 years, there may be considerable local vascular damage, if the coarctation is severe, precluding favorable results. A comparatively long and tapering segment of stricture, or a high position, adjacent to the subclavian artery, makes end-to-end anastomosis of the resected aorta not feasible. In eight of his cases, the author deemed it advisable to ligate the aorta at the stricture, section it distally, and then accomplish anastomosis with the rotated proximal end of the sectioned left subclavian artery. Results in these instances were not so good as was hoped.

In thirteen cases, resection of the stenosed portion followed by end-to-end anastomosis was carried out. There were five deaths in the entire group. The results seem satisfactory in twelve of the sixteen patients who survived operation.

ARKLESS.

McMillan, G. C., and Duff, G. L.: Mitotic Activity in the Aortic Lesions of Experimental Cholesterol Atherosclerosis of Rabbits. Arch. Path. 46:179 (Aug.), 1948.

The authors were impressed by the occurrence of mitotic configurations in the foam cells of the aortic lesions induced in rabbits by cholesterol feeding. They found clearly definable mitoses in the atheromatous foam cells in six out of ten rabbit aortas. Photographic evidence revealed various phases, all undoubtedly mitotic. They were found not only in the superficial but also in the deep cellular deposits of the atheroma. Their presence is indicative of the origin of numerous large binucleate foam cells in the deeper layers of the intimal lesions.

Regardless of the origin of the foam cells in general in these aortic lesions, it is clear that there is a large local proliferation. The mitotic process was not found in the lining of endothelial cells, and it is clear that the process was activated in cells that had already infiltrated into the atheromatous focus.

GOULEY.

Potts, W. J., Gibson, S., and Rothwell, R.: Double Aortic Arch. Report of Two Cases. Arch. Surg. 57:227 (Aug.), 1948.

The authors report two cases and describe the characteristic clinical signs of a double aortic arch. These signs include laryngeal stridor, noisy, labored respiration, dysphagia, frequent infections of the upper respiratory tract, and choking spells often associated with cyanosis. These recurring symptoms in an infant should make one suspicious of a constricting double aortic arch. The suspected diagnosis can be established fluoroscopically and roentgenologically. With the infant in a lateral position on the fluoroscopic table barium sulfate will help demonstrate a concave shadow in the posterior wall of the esophagus.

BECK.

Mussafia, A., and Masini, V.: Prognosis in Myocardial Infarction. I. Prognosis After the Acute Stage. Study of 100 Cases. Cuore e circolaz. 32:193 (Aug.), 1948.

The authors studied a series of one hundred patients who survived the acute stage of myocardial infarction. They were divided into three groups: (1) Patients with good functional recovery (57 per cent); (2) patients with resulting angina pectoris (23 per cent); and (3) patients with resulting cardiac failure (20 per cent). The prognosis depends on the age of the patient, on the previous cardiovascular condition, and on the severity of the infarction. In many cases the patient survived the infarction for several years (more than eight). The causes of death are cardiac failure or coronary insufficiency (usually a new infarction). Failure is more common in hypertensive patients and/or in patients who suffered from failure before the infarction. Recurrence of the infarction is unpredictable and may occur also in patients of the first group even many years after the first attack.

LUISADA.

Lazzari, G.: Acute Malignant Endocarditis From Pneumococcus. Cuore e circolaz. 32:201 (Aug.), 1948.

A case of acute pneumococcic endocarditis in a 20-year-old man is described. The condition failed to respond to penicillin treatment, but was cured after streptomycin administration. Initially 10,500,000 units of penicillin over a period of seventeen days were administered without any result. After administration of 6.0 Gm. of streptomycin (in eight days) the patient improved considerably; however, the treatment had to be discontinued for lack of the drug. Penicillin was resumed (6,000,000 units in fifteen days) and the patient became worse again. Flat temperature and cure followed a renewed administration of streptomycin (0.5 Gm. twice daily) in spite of complicating pulmonary embolism and bronchopneumonia.

The patient was followed for five months from the beginning of the disease, and received 21,000,000 units of penicillin and 21 Gm. of streptomycin.

LUISADA.

Ochsner, A.: Venous Thrombosis. Surgery 24:445 (Sept.), 1948.

The author reviews the evidence for the view, popularized by him and his associates, that it is necessary to differentiate two types of venous thrombosis, namely, thrombophlebitis and phlebothrombosis. In the diagnosis of phlebothrombosis, he calls attention to a sign which helps distinguish between inflammatory lesions of the skin and subcutaneous tissues of the back of the leg and phlebothrombosis. After the presence of tenderness has been determined by the application of pressure anteriorly against the calf, pressure is then exerted from side to side. In the presence of phlebothrombosis, the last maneuver should cause no pain.

With regard to treatment of these conditions, the author continues to advocate repeated paravertebral sympathetic blocks for the acute stage of deep thrombophlebitis and bilateral superficial femoral vein ligation for phlebothrombosis.

ABRAMSON.

De Takats, G., Julian, O. C., and Fowler, E. F.: The Surgical Treatment of Essential Hypertension. IV. Case Selection and Technique as Influencing Results. Surgery 24:469 (Sept.), 1948.

The authors present the results of sympathectomy in the treatment of 250 patients with hypertension. These were divided into three categories. Group I consisted of patients below the age of 40 years, in whom minimal or no detectable organic damage could be determined. These individuals demonstrated normal blood pressure on complete rest or with barbiturates. Group II consisted of patients whose ages varied from 20 to 55 years, but in whom moderate vascular sclerosis was noted in all organs. There was also well-demonstrated angiospasm. The diastolic blood pressure could not be lowered below 110 mm. Hg by any means, this reading showing a definite tendency to increase in the last six months. In Group III were placed those individuals with a marked degree of involvement, demonstrating large, recurrent retinal hemorrhages and exudates or papilledema, high, fixed diastolic blood pressure, not capable of being lowered below 120 mm. Hg, congestive or anginal heart failure, poor renal function, and numerous cerebrovascular accidents.

Contraindications to operation consisted of extensive organic damage to brain, retina, heart, or kidneys, mechanical obstruction to circulation, marked psychic involvement, and obvious pituitary corticoadrenal activity.

The results following sympathectomy were excellent in the first group, fair in the second, and poor in the third.

ABRAMSON.

Shumacker, H. B.: Causalgia. III. A General Discussion. Surgery 24:485 (Sept.), 1948.

The author reviews the early and recent contributions to the problem of causalgia. With regard to treatment, he emphasizes the importance of sympathetic interruption, especially through the use of sympathectomy. The various theories concerning the mechanism of initiation and persistence of pain in this condition are also presented. Of the two most widely accepted views, one assumes the existence of an irritative focus resulting from the trauma, with afferent impulses arising from this trigger point which set up an abnormal state of activity in the spinal cord. This results in the initiation of abnormal motor responses from both lateral and anterior horn neurons. Relief from sympathetic interruption is explained on the basis of a break in the vicious arc. The second theory explains the pain of causalgia as due to alteration in the excitability of adjacent sensory fibers by the continuous sympathetic impulses.

ABRAMSON.

Scotti, T. M., and McKeown, C. E.: Sarcoidosis Involving the Heart in a Case of Sudden Death. Arch. Path. 46:289 (Oct.), 1948.

A case of sarcoidosis of the heart which resulted in sudden death is reported. The patient, a 26-year-old Negro man, had complained of precordial pain eighteen months previously; the pain had soon subsided. Otherwise his medical history had been negative, and death was entirely unexpected.

Autopsy revealed sarcoidosis of the tracheobronchial lymph nodes, and to a lesser degree of the mesenteric nodes. Otherwise, only the heart showed significant involvement. Nodules in the epicardial fat and in the myocardium, notably in the left atrium, the interventricular septum, the papillary muscles, and throughout the wall of the left ventricle, were identified as

typical sarcoid lesions. Aside from these, a dense hyalinized tissue replaced muscle in many areas. This fibrosis was a residuum of healed sarcoidosis.

The authors, in reviewing the recorded instances of cardiac involvement in this disease, emphasize that sudden death has been previously noted, and that when a clinical diagnosis of systemic sarcoidosis has been established, a persistent tachycardia in the absence of fever indicates cardiac involvement. GOULEY.

Anromin, G. D., Schlichter, J. G., and Solway, A. J. L.: Medionecrosis of the Aorta.
Arch. Path. 46:380 (Oct.), 1948.

The authors believe that the status of the vasa vasorum is an important factor in the development of ischemia of the media of the aorta, and that in some cases it may be the sole determining factor. They consider dissection of the medial coat as an infarction. Experimentally, any mechanism, chemical or mechanical, that may reduce the nutrient capacity of the vasa vasorum can lead to dissecting aneurysm.

The authors injected radiopaque material at autopsy into the body of a patient with an antemortem diagnosis of dissecting aneurysm; also into the bodies of patients dying from other causes. In the presence of a dissecting aneurysm the vasa vasorum could not be visualized. In the uninvolved portions of this aorta the vasa vasorum were filled with radiopaque material. Near the perforation their lumina were almost obliterated by medial and intimal thickening.

In the course of this study the authors examined the aortas of many patients with hypertension, and were able to confirm previous findings of other investigators, namely, that the vasa vasorum frequently show medial hypertrophy and intimal hyaline thickening. GOULEY.

Pantridge, J. Frank: Cardiac Lesions in Thiamin Deficiency. *Brit. Heart J.* 10:252 (Oct.), 1948.

Contrary to the general impression, experience with beriberi in British and Australian prisoners of war indicated that the occurrence of heart block was not infrequent. For this reason, an analysis was made of the effects upon cardiac conduction of prolonged, severe thiamin deficiency in four pigs, with two additional pigs used as controls. The standard leads and CF₄ were used.

On the thirtieth to the fortieth day, the four thiamin-deficient pigs developed A-V conduction disturbances. A single injection of 25 mg. of thiamin hydrochloride prevented the death of three pigs with block.

At autopsy, excess fluid was found in the pericardial sacs. There was dilatation of the right auricle and right ventricle, particularly the pulmonary conus. Microscopically, lesions were found in the auricles, the auricular appendages, and the auricular septa. These lesions consisted of regions of active necrosis of muscle with leucocytic and erythrocytic infiltration, edema of the reticulum, and in one animal surviving 157 days, areas of replacement of muscle by granulation tissue or fibrous tissue. Marked degenerative changes were seen in many of the cells of the conducting system. An acute hyaline necrosis was seen in the Purkinje cells. SOLOFF.

Allen, A. W., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism.
Bull. New York Acad. Med. 24:619 (Oct.), 1948.

The authors point out certain conditions which are conducive to venous thrombosis: low environmental temperature; cardiac conditions requiring quiet, sedation, and bed rest in a sitting position; extensive malignancy involving the abdominal viscera particularly; acute intra-abdominal infections; general debilitation; infirmity, with its influence on muscular activity; and trauma and burns involving the lower extremities.

One of the most important measures in the prevention of venous thrombosis is the counter action of stasis in the legs by posture, compression bandages, and active or passive exercises. The authors prescribe prophylactic superficial vein interruption in the depleted, very ill patient with advanced carcinoma or infection, or in patients with injuries to the lower extremities in whom immobilization is necessary. Nevertheless, they state that Dicumarol is likewise effective in such patients in reducing the incidence of thrombosis. ABRAMSON.

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AMERICAN HEART ASSOCIATION ANNUAL MEETING, JUNE 22-25, 1950

The next Annual Meeting and Scientific Sessions of the Association will be held June 22-25, 1950, at the Fairmont Hotel, San Francisco. Early reservations are advised and arrangements should be made directly with the hotel, stating the type of accommodations required and giving specific dates of arrival and departure.

Dr. Louis E. Martin, of Los Angeles, to whom applications and inquiries should be sent in respect to papers for inclusion on the program, is Chairman of the Program Committee for the Scientific Sessions. Dr. Meyer Friedman of San Francisco is Chairman of the Program Committee of the Section on the Circulation. The remainder of the Committee will be announced at a later date.

The first Scientific Session is scheduled for Thursday afternoon, June 22. The annual meeting of the Assembly will be held Saturday afternoon, June 24 and the annual dinner the same evening.

INTERNATIONAL CONGRESS IN 1950

The First International Congress on Cardiology will be held in Paris, France, September 3-9, 1950. Arrangements for transportation and hotel accommodations may be made by addressing Mr. Gabriel Reiner, Cosmos Travel Bureau, Inc., 40 West 45th St., New York 19, N. Y., or any other travel agency. Anticipated heavy bookings next September make it advisable to secure early tentative reservations, which are not binding until a later date. Professor Charles Laubry of Paris is the General Chairman of the Congress.

NEW AFFILIATED HEART ASSOCIATIONS

The affiliation of the Nebraska Heart Association, South Carolina Heart Association, Orange County (N. Y.) Heart Association, Western Pennsylvania Heart Association, Florida Heart Association, and the State Tuberculosis and Health Committee for the State Charities Aid Association, New York, has been completed.

Other associations which will be affiliated soon are: Pennsylvania Heart Association, Kentucky Heart Association, Western New York Heart Association, Colorado Heart Association, New Mexico Heart Association, North Carolina Heart Association, Montana Heart Association, and the East Tennessee Heart Association.

American Heart Journal

VOL. 38

NOVEMBER, 1949

No. 5

Original Communications

CALCIFICATION AS A DIAGNOSTIC SIGN OF SYPHILITIC AORTITIS

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CALCIFICATION of the aorta, particularly the knob, is commonly seen in roentgen studies of the chest. Little attention is usually paid to this finding other than to note its presence. Calcification of the ascending aorta alone, or with calcification of the knob, was noticed with sufficient regularity in cases of syphilitic aortitis studied roentgenologically at the Los Angeles County General Hospital to stimulate interest in its significance. Of thirty-eight unselected cases of syphilitic aortitis referred for study during a nine-month period, nineteen (50 per cent) showed calcification of the thoracic aorta and fifteen (39.4 per cent) showed calcification of the ascending aorta alone.

In atherosclerosis of the aorta the most advanced lesions are found usually in the abdominal portion. The thoracic aorta is usually less severely affected, but it is frequently more or less markedly involved. Atheromatosis usually begins at the mouths of the intercostal arteries and spreads peripherally. The base of the aorta is often relatively intact except in very severe cases.¹⁻⁴

The significance of atherosclerosis in relation to syphilitic aortitis has not been well appreciated in spite of the fact that as early as 1925 Anitschkow⁵ pointed out that syphilitic infection of the aortic wall predisposed to the development of atheromatous lesions in the intima. In the late stages of this process this is often very evident. The intima is very thick and fibrous, with fatty spots in its depth that tend to disintegrate and to become calcified.

Atheromatosis with calcification of the aorta has usually been considered as a coincidental finding. Christian⁶ has stated that "calcification and intimal ulceration are infrequent in syphilitic aortitis, but often arteriosclerosis is combined, and in the arteriosclerotic lesions calcification and ulceration are frequent." Boyd² was struck by the frequency with which atheromatous lesions are found in the intima and stated that, although syphilis is not a direct cause of atheroma, it may act as a predisposing factor. Bell³ did not mention the connection between

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arteriosclerosis and syphilitic aortitis other than to state that "when arteriosclerotic changes are also present (atheroma and calcification) the picture becomes complicated and more difficult to recognize." Mallory,⁴ on the other hand, in a discussion of a case stated that "the aorta was markedly sclerotic, diffusely dilated, wrinkled, and scarred in spots between the atheromatous plaques. The entire process was most marked in the thoracic portion of the aorta, diminishing as one proceeded toward the abdominal portion, which is characteristic of syphilis and in contrast to ordinary arteriosclerosis." Forbus⁷ has pointed out also that the syphilitic process stops quite abruptly at the lower level of the arch, a common and characteristic occurrence.

The characteristic findings in the aorta in syphilis and arteriosclerosis can be illustrated by the two brief case histories which follow.

Fig. 1 is an illustration of the aorta of a 69-year-old patient with a diagnosis of syphilitic aortitis. The aorta shows the typical longitudinal "tree-bark" wrinkling and atheromatosis which involved the ascending aorta and arch and abruptly ended at the junction of the arch and descending aorta. Fig. 2 is a post-mortem x-ray film of this aorta showing the calcification laid down in an interlacing manner which follows the pattern of longitudinal wrinkling. The interlacing network, when caught on end, produces a linear shadow, which explains the linear type of calcification seen in the ascending aorta in ante-mortem x-ray films. Fig. 3 is the ante-mortem roentgenogram of the patient whose aorta is depicted in Figs. 1 and 2.

Fig. 4 is an illustration of the aorta of a 70-year-old patient with typical atherosclerosis of the aorta. The ascending aorta is smooth and free of atheromata. In the arch and descending aorta the atheromatosis is marked. Fig. 5 is the post-mortem film of this aorta showing spotty calcified plaques in the arch with calcification most marked about the orifices of the arteries as they leave the aorta.

With the difference in localization of the atheromatosis in the aorta in arteriosclerosis and syphilis, it was felt that demonstration of calcification in the different portions of the aorta should be of value in the differential diagnosis of these two conditions. Review of the literature and the textbooks of roentgenology has revealed little comment or agreement on this subject. Mallory and Schatzki⁴ and Bland and Mallory⁸ have stated that calcification is an important clue to the presence of syphilitic aortitis and more indicative of the disease than against it. Sproul⁹ mentioned identification of calcification in the aorta and showed a case with marked involvement of the ascending aorta but made no special comment. Schwedel¹⁰ stated that calcification of the aortic arch is due most often to arteriosclerosis, although it is frequently associated with syphilitic aortitis. He felt that calcification may be considered as evidence of past damage but is not of itself diagnostic of syphilitic aortitis, nor of prognostic significance. He also pointed out that calcification of the aorta is absent in the stage of dynamic dilation but is not infrequent when the static stage is reached. Roessler¹¹ stated that "it may be a difficult matter at necropsy to distinguish between atheroma of the aorta and syphilitic aortitis because syphilitic aortitis is very frequently accompanied by atheromatous changes in the aorta." He



Fig. 1.—Post-mortem specimen of syphilitic aortitis.



Fig. 2.—Post-mortem x-ray film of aorta shown in Fig. 1.

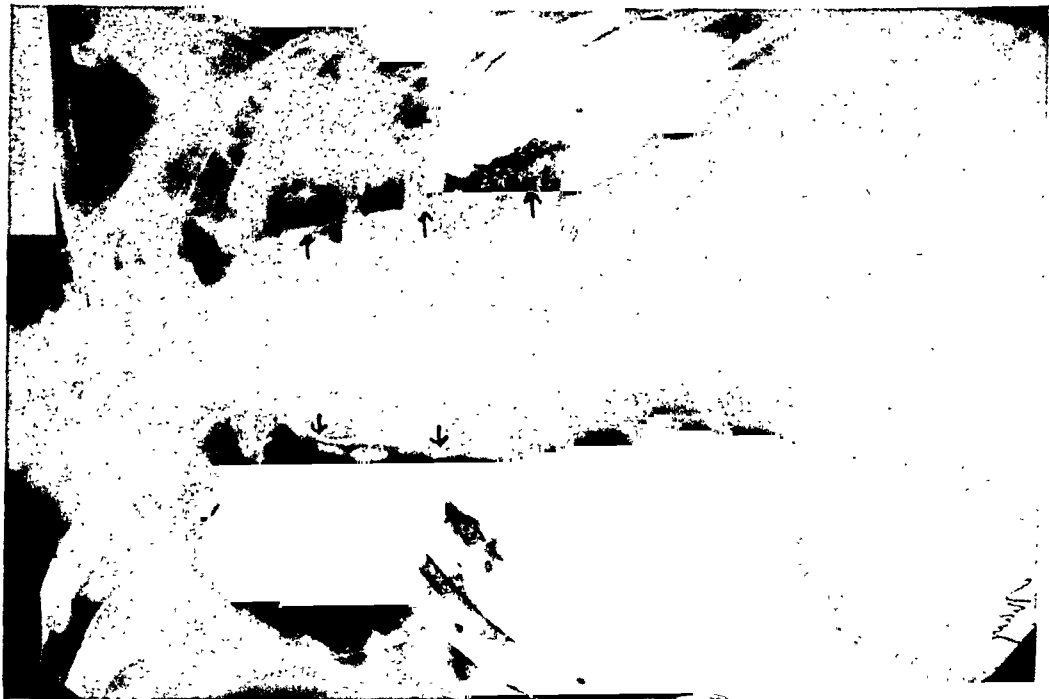


Fig. 3.—Ante-mortem x-ray film of aorta shown in Figs. 1 and 2.



Fig. 4.—Post-mortem specimen of atherosclerosis of aorta.

showed several illustrations of roentgenograms which revealed calcification, but except for mentioning the presence of lime salt deposits, he made no statement as to its significance.

The only controlled study found was one made at the Cleveland City Hospital by Jackman and Lubert,¹² who gave comparative figures in sixty-six cases of syphilitic aortitis and sixty-two cases of severe atherosclerosis of the



Fig. 5.—Post-mortem x-ray film of aorta shown in Fig. 4.

thoracic aorta. They found calcification of the ascending aorta in 22.7 per cent of the cases of syphilitic aortitis, as compared with 3.2 per cent of the cases of severe atherosclerosis. They concluded that linear calcification of the ascending aorta is a valuable sign of syphilitic aortitis.

MATERIAL AND OBSERVATIONS

A review was made of all cases of syphilitic aortitis that came to autopsy at the Los Angeles County General Hospital from December, 1938, to July, 1947. Of a total of 400 cases, films of 122 patients with roentgenographic studies prior

Horlick, L., and Katz, L. N.: The Effect of Diethylstilbestrol on Blood Lipids and the Development of Atherosclerosis in Chickens on a Normal and Low Fat Diet. J. Lab. & Clin. Med. 33:733 (June), 1948.

The implantation of stilbestrol pellets in young chickens resulted in a marked hyperlipemia and hypercholesterolemia while on a normal diet and on a specially prepared low fat diet. After stilbestrol implantation, chickens on the normal diet developed a somewhat higher cholesterolemia than did the chickens on the low fat diet. Atherosclerosis of the induced type was observed in a high proportion of the stilbestrol-treated chickens in both the group receiving the normal diet and the group receiving the low fat diet. Spontaneous atherosclerosis occurred in 40 per cent of the chickens used as normal controls, but it occurred in none of the control group which was placed on a low fat diet. The authors state that stilbestrol probably acts to produce atherosclerosis through its cholesterolemic effect.

KLINE.

Slaughter, O. L., Brown, H. S., and Wakim, K. G.: Effects of Tetraethylammonium Chloride on Blood Flow in the Extremities of Man. J. Lab. & Clin. Med. 33:743 (June), 1948.

The purpose of this study was to determine the effect of tetraethylammonium chloride on the blood flow in the upper and lower extremities of healthy human subjects exposed to relatively warm environment (temperature ranging between 80° and 85° F.) and to establish a basis for comparison with subsequent studies on various abnormalities of the vascular system in patients.

Tetraethylammonium chloride was given intravenously to seven healthy adults. The effects of the drug were studied plethysmographically by the use of the compensating spirometer recorder. In the presence of vasodilatation due to a relatively warm environment of 80° to 85° F., tetraethylammonium chloride produced an average increase in blood flow of 100 per cent in the forearms and 135 per cent in the legs. In addition to the increase in blood flow, disturbances of vision with impairment of accommodation, metallic taste and dryness of the mouth, and increase in heart rate occurred after injection of tetraethylammonium chloride.

KLINE.

Fastier, F. N., and Smirk, F. H.: Some Properties of Amarin, With Special Reference to Its Use in Conjunction With Adrenaline for the Production of Idio-ventricular Rhythms. J. Physiol. 107:318 (June), 1948.

The circulatory effects of Amarin, a cyclic amidine derivative, were studied in dogs by a number of mechanical devices, including motion pictures, electrograms, myocardiographs, oscillography, etc., and by direct observation. This compound causes a profound bradycardia with lengthening of the P-R and QRS-T durations, occasionally to three times the normal, by a nonvagal effect. In larger doses the heart beat may originate from the A-V node or from a ventricular focus. Various types and degrees of heart block were noted, as were such abnormalities as the independent contraction of the auricles, the driving of the auricles by the ventricles, electrical alternation, and changes in S-T segment and T waves. Small doses exert a pressor action by peripheral vasoconstriction. Larger doses may produce circulatory collapse with cardiac dilatation and arrest.

After Amarin the pressor responses to small doses of epinephrine are greatly increased in the anesthetized animal. Ventricular flutter could be readily produced by moderate doses of epinephrine. When this was observed directly, a series of peristalsis-like waves succeeded each other over approximately the same course on the ventricular surface; two or three waves could be seen at one time and these did not originate from any single point. It would seem that the refractory period was shortened, and flutter would develop after a new excitatory wave began before the preceding ventricular wave had ended. Just before flutter develops, one may see an R wave superimposed on a T wave. This is probably an extreme instance of an increase in duration of ventricular systole relative to that of diastole.

Under Amarin, ventricular fibrillation appeared as many small wavelets running in different directions. Many regions of the ventricles showed regular cycles of mechanical movement which

serology, confirm the impression that as the duration of the syphilitic process increases, the positive serology tends to diminish, and the atheromatosis with calcification of the ascending aorta increases.

The presence of aortic insufficiency, found either clinically or at necropsy, appears to have no significant relationship to the calcification process. Insufficiency was present in 45.4 per cent of the patients with calcification and in 36 per cent of the syphilitic patients without calcification. This differs considerably from the data given in the Cleveland report in which insufficiency was found in only 13.3 per cent of the patients showing calcification and in 39.2 per cent of the patients in whom no calcification was found.

Tables I and II summarize the findings arrived at by both clinics.

DISCUSSION

The difference in the elective localization of the atheromatosis in the thoracic aorta in syphilis and arteriosclerosis has been demonstrated. As the lesions progress, with the deposition of lime salts in the atheromatous plaques, roentgenographic demonstration of the presence of calcification in the different portions of the aorta should give valuable clues as to the etiology of the underlying processes. It must be emphasized that this is a late sign in syphilitic aortitis and of no value in the early diagnosis, which can only be made by careful and repeated examination of the type of pulsation in the ascending aorta as demonstrated by fluoroscopic examination^{13,14} and by application of diagnostic criteria as laid down by Maynard¹⁵ and Woodruff.¹⁶

Inasmuch as the walls of the aorta are in constant motion, slow exposures used on routine chest films will blur the calcifications and make their detection difficult or impossible. Very rapid exposures (1/20 to 1/30 second), using sufficiently heavy exposure to reveal detail in the cardiomedial opacity (usually obtained by high kilovoltage), will detect the lime salt deposits early. In the present series, 20 per cent of the patients in the noncalcific group showed calcification at autopsy which was not detected by the routine film techniques used. In only eight cases of the twenty-two with calcification detected by x-ray was calcification mentioned by the pathologist in the autopsy protocol. In view of these findings, it is felt that a considerably higher incidence of positive roentgenograms can be accomplished by the improved techniques and can be made to approach the figures of 39 to 50 per cent obtained in the clinical cases which prompted this study.

The posteroanterior position will show almost all positive cases, although frequently the left anterior oblique position is more satisfactory. In this view the calcification is present in the ascending aorta 20 to 30 mm. inside the vascular shadow and is seen within the cardiac shadow, starting in the region of the aortic valve. Fig. 6 demonstrates marked calcification of this type, as seen in the left oblique position.

The presence of calcification of the ascending aorta in 18 per cent of the syphilitic cases, as compared with only 2 per cent in the arteriosclerotic series, makes the roentgenographic demonstration of calcification a significant factor in the diagnosis of syphilitic aortitis even with the absence of positive serology,

were not necessarily repeated in the same direction, nor were they of equal strength. Thus, ventricular fibrillation, under these conditions, did not appear to depend on any simple system of circus rhythms. Flutter induced by Amarin and epinephrine was probably due to multiple circus rhythms.

WAIFE.

Konzett, H., and Verney, E. B.: Observations on the Urine, Blood and Arterial Pressure of Dogs Before and After the Production of Renal Ischemia. J. Physiol. 107:336 (June), 1948.

These investigators were unable to confirm the report of Lockett (J. Physiol. 105:126, 1946) that a new base, termed α , was present in the urine of dogs after the production of renal ischemia. Lockett claimed that this base is absent in normal animals, that it appears in the urine within ten minutes following renal artery compression, that it is excreted mainly by the normal renal cortex, and that a clear relation exists between the presence of this substance and hypertension. On the contrary, these authors found that a color test for the α substance was positive in normal urine, and no increase was noted after renal artery obstruction. Piperidine in the dog's urine gives the same color reaction as the postulated α substance.

WAIFE.

Ogilvie, T. A., Penfold, J. B., and Clendon, D. R. T.: Gangrene Following Intra-arterial Injection of Myanesin. Lancet 254:947 (June 19), 1948.

A 67-year-old woman was admitted to the hospital with a provisional diagnosis of neoplasm of the stomach. Laparotomy revealed a gall bladder with thickened walls surrounded by many adhesions and cholecystectomy was performed. During the operation 10 ml. of 10 per cent Myanesin was injected into the median basilic vein to obtain muscular relaxation. The same day the right forearm and hand were much discolored, deeply cyanosed, and of marble coldness; but a good radial pulse was easily palpable at the wrist. A brachial plexus block was performed with procaine, but the circulation did not improve. Next day the hand and forearm were still blue, cold, and functionless, although there was a good radial pulse. A cervical sympathetic block was done, but though the fingers may have been slightly warmer for a short time, after this procedure they were still deeply cyanosed.

Two days later the arm was blue, cyanosed, and cold from the finger tips to the elbow, the nails being almost black. The brachial artery was exposed opposite the elbow joint; the wound bled freely above the elbow, but did not bleed below the joint level, and the superficial veins were collapsed. No thrombosis was present in the brachial, radial, or ulnar artery. The gangrene of the hand and forearm progressed, but the patient's general condition gave no cause for anxiety. The arm was amputated three inches above the elbow joint. The upper end of the brachial artery showed unorganized ante-mortem thrombus attached to the intima.

Subsequent experimental studies revealed that the curdling observed was not due to the effect of Myanesin on the blood, plasma, serum, or heparin, but that there was an alteration in the physical state of the Myanesin with its subsequent precipitation from solution by some constituent or constituents of the blood. It is possible, therefore, that the gangrene in this case can be explained by the profound change which takes place when blood and Myanesin are mixed.

It is possible that, in spite of adequate skill and care in making the injection, some of the solution was injected into the brachial artery instead of into the median basilic vein.

BELLET.

TABLE II. SUMMARY OF THE FINDINGS ARRIVED AT BY THE CLINICS AT THE LOS ANGELES COUNTY GENERAL HOSPITAL AND THE CLEVELAND CITY HOSPITAL

	COLOR		SEROLOGY		AORTIC INSUFFICIENCY	
	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL
Syphilitic calcific group (Calcification in ascending aorta)	19 white	10 white	Pos. 16	Pos. 9	10 present	2 present
	5 Negro	5 Negro	Neg. 5	Neg. 3	12 absent	13 absent
			Doubt. 1	None 3		
Arteriosclerotic calcific group	2 white	2 white	Pos. 1	Pos. 1	0 present	1 present
	0 Negro	0 Negro	Neg. 1	Neg. 1	2 absent	1 absent
Syphilitic noncalcific group	79 white	24 white	Pos. 86	Pos. 40	36 present	20 present
	21 Negro	27 Negro	Neg. 10	Neg. 9	64 absent	31 absent
			Doubt. 3	None 2		
Arteriosclerotic noncalcific group	96 white	54 white	Pos. 3	Pos. 6	1 present	0 present
	2 Negro	6 Negro	Neg. 88	Neg. 54	97 absent	60 absent
			None 7			

On May 8 the arrhythmia was first diagnosed as auricular flutter with a ventricular rate of 190. A review of the tracing, however, indicates the arrhythmia to be auricular paroxysmal tachycardia at a little slower rate. Aside from the ventricular rate, which is rare for auricular flutter, there is a definite isoelectric segment present in Lead III. This has been emphasized by Decherd and Herrmann as the one dependable criterion for the differentiation of the two tachycardias in questionable cases. The patient's condition was so desperate, because of the continued tachycardia, that it was decided to give quinidine by vein. On May 9, 22 grains of quinidine dissolved in 400 c.c. of isotonic saline solution were administered. The tachycardia persisted and the electrocardiogram showed auricular paroxysmal tachycardia on May 10 (Fig. 6). The next day, May 11, the rhythm was normal but the patient had diffuse pulmonary edema, then developed pneumonia, and died two days later, May 13, 1940. Apparently heroic therapy in this case was useless, and death was ascribable to an uncontrolled ventricular rate of 200 per minute for four days.

Comment.—Although transitions from auricular fibrillation to auricular flutter are not uncommon in heart disease, transitions from auricular paroxysmal tachycardia to flutter or fibrillation are relatively uncommon. It apparently is a grave prognostic omen. Eight of the fourteen patients reported by Decherd and Herrmann died soon after they were observed. In only one was the diagnosis of myocardial infarction established.

DISCUSSION

Supraventricular paroxysmal tachycardia obviously is not an arrhythmia that is attributable to serious arteriosclerotic heart disease since it is found so rarely in myocardial infarction. It is true, however, that it occurred in the patients of our series with marked, long-standing heart damage. Probably all of these patients had had previous infarcts, and coronary atherosclerosis and ischemia were extreme. It is interesting and possibly significant that Rosenbaum and Levine found no instances of auricular paroxysmal tachycardia in their group of patients who presumably were suffering from their first attack. Master, Jaffe, and Dack⁸ said that heart failure was present in all of their cases. It is apparent, therefore, that supraventricular tachycardia in relation to myocardial infarction is an arrhythmia which appears usually in those patients with extensive, long-existent heart damage.

Its appearance becomes of serious prognostic significance. Sinus tachycardia, which involves a ventricular rate only slightly over 100, is known to increase the mortality.^{9,10} In a recent study of 572 patients at the Michael Reese Hospital, the mortality of the entire group was found to be 21.8 per cent. In the group with congestive failure, the mortality was 41.9 per cent. Mintz and Katz observed that "the combination of tachycardia and congestive failure is of graver prognostic significance than either alone." The greater load of a faster ventricular rate such as is produced by supraventricular tachycardia obviously should increase the mortality even more than sinus tachycardia, and it apparently does.

The gravity of supraventricular tachycardia should depend largely upon the degree of pre-existing damage and upon the duration of the tachycardia. Master and his co-workers found nine instances of paroxysmal tachycardia occurring in 300 patients with coronary artery thrombosis. All nine patients had heart failure and had an enlarged heart and hypertension. Of these, five were identified as supraventricular in origin by electrocardiographic tracings. One was

for it has been demonstrated that as the disease progresses in age, calcification becomes more prominent and the incidence of positive serology decreases.

The youngest patient in the nonsyphilitic groups of both series was a 60-year-old man; the average age was 72.7 years. In the syphilitic group the youngest age represented was 32 years and the average age was 58 years. It must be remembered that syphilis is a disease which is usually acquired early in life, and, therefore, in spite of the fact that the average duration of the disease in patients showing calcification was 34.6 years, calcification is found earlier in life in syphilitic patients, than in the arteriosclerotic group. Demonstrable calcification in patients under 60 years of age is strong evidence that the underlying process is syphilis.

The presence of calcification of the ascending aorta is of value in the differential diagnosis of aortic insufficiency as to rheumatic, syphilitic, or arteriosclerotic etiology. Fig. 7 illustrates a case in point (H. R. 974-471). The patient was a white man, 43 years of age, who entered the hospital in July, 1946. Aortic systolic and diastolic murmurs and a mitral systolic murmur were present. One examiner also heard an apical diastolic rumbling murmur. The patient gave the history of having had syphilis twenty years previously which had been adequately treated. The serology was negative. It was felt that this was a case of combined rheumatic valvular disease until x-ray study revealed calcification of the entire thoracic aorta of marked degree. The patient came to necropsy approximately one year later. There was no evidence of old or recent rheumatic valvulitis. The dilated aorta showed marked scarring typical of syphilis and superimposed atherosclerosis from the aortic ring to the diaphragm.

Calcification of the ascending aorta is also of value in distinguishing thoracic aneurysms from neoplasms. The presence of calcification implies the presence of syphilis which may swing the balance in favor of the diagnosis of syphilitic aneurysm. This is particularly true in the case of aneurysms of the abdominal aorta. It has long been known that most abdominal aneurysms are arteriosclerotic in origin.¹⁷ In the present study 2.2 per cent of the syphilitic patients had abdominal aortic aneurysms (9 in 400 cases), as compared with 4.1 per cent in the arteriosclerotic series (36 in 801 cases). In Fig. 8 is shown the heart and aorta of a patient with an abdominal aneurysm in which calcification of the ascending aorta helped to demonstrate the syphilitic etiology. The patient (P.G. 708-932) was a white man, 53 years of age, admitted to the hospital in August, 1943, with the chief complaint of pain in the lumbar area which had been present for twenty-five years. He developed a penile lesion in 1910 with a positive Wassermann and received antisyphilitic therapy for two years. Another course of treatment of two years' duration was given from 1938 to 1940. Examination revealed an old acid-fast process in the lungs, a blood pressure of 145/90, no cardiac enlargement, and apical and aortic systolic murmurs. X-ray examination of the abdomen showed marked calcification of the abdominal aorta. Marked destruction of the bodies of the first and second lumbar vertebrae was present with curvilinear calcification, 9.0 cm. in diameter, projecting to the left and ventrally from the spine just above the area of vertebral destruction. The diagnoses considered were Pott's disease with old, calcified, soft-tissue abscess

5. Master, A. M., Dack, S., and Jaffe, H. L.: Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, *Ann. Int. Med.* 11:735, 1937.
6. Decherd, G. M., and Herrmann, G. R.: The Association of Paroxysmal Atrial Tachycardia With Atrial Flutter or Fibrillation, *AM. HEART J.* 28:457, 1944.
7. Decherd, G. M., and Herrmann, G. R.: Paroxysmal Supraventricular Tachycardia With A-V Block, *AM. HEART J.* 26:446, 1943.
8. Master, A. M., Jaffe, H. L., and Dack, S.: The Treatment and the Immediate Prognosis of Coronary Artery Thrombosis (267 Attacks), *AM. HEART J.* 12:549, 1936.
9. Levine, S. A., and Brown, C. L.: Coronary Thrombosis; Its Various Clinical Features, *Medicine* 8:245, 1929.
10. Master, A. M., Dack, S., and Jaffe, H. L.: Coronary Thrombosis; an Investigation of Heart Failure and Other Factors in Its Cause and Prognosis, *AM. HEART J.* 13:330, 1937.

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Book Reviews

DIAGNOSTICO DAS FORMAS ANATOMO-CLINICAS DA CARDITE REUMATICA. By E. Magalhães Gomes, M.D. Rio de Janeiro, 1947, Rodriguez and Co., 345 pages and 65 figures.

This book is a comprehensive study of reumatic disease with special regard to rheumatic carditis. The disease is considered to be an infectious process with allergic reactions to the proteins of *Streptococcus hemolyticus*.

The diagnosis of the disease is studied with particular attention. Among the laboratory data, the Weltmann reaction is considered to be very accurate, a conclusion which should be accepted with reserve. The various possible complications of rheumatic disease are studied in detail. These include renal, pleuropulmonary, hepatic, thyroid, ocular, and neurological disturbances. The study of cardiac manifestations is completed by the description of clinical cases and the presentation of excellent electrocardiographic, phonocardiographic, and roentgenologic documentation.

This monograph should find its place in the library of all centers for the study of rheumatic fever.

A. LUISADA, M.D.

LA PATHOGENIE DES ALTERATIONS ELÉCTROCARDIOGRAPHIQUES DE LA PÉRICARDITE. By E. Coelho, M.D. Lisbon, 1947, Bertrand, Ltd., 74 pages and 58 figures.

This monograph reports studies of the electrocardiograms in 138 cases of pericarditis. These include examples of uremic, tuberculous, purulent, and rheumatic types; hemopericardium and calcific and constrictive pericarditis are also studied.

Only six cases presented a normal electrocardiogram; in all others electrocardiographic changes were observed, at least in certain phases of the disease. The diagnostic value of the electrocardiogram was found to be high; in certain cases, fever and electrocardiographic changes were the only signs, and paracentesis of the pericardium confirmed the diagnosis. According to the author, there is no single type of electrocardiographic change and no typical evolution.

The electrocardiogram is of no help in making an etiological diagnosis. However, upward displacement of RS-T segment with high take-off of the T wave was found only in purulent and rheumatic pericarditis and never in tuberculous pericarditis. The deeply inverted T wave, encountered in certain cases of uremic pericarditis, is considered as a pre-existing change and sometimes the result of high potassium content of the blood.

In certain cases of associated rheumatic pericarditis and associated myocarditis, the electrocardiogram may contribute to the etiological diagnosis.

The evolution of the electrocardiogram varies in each type of pericarditis; the changes may persist indefinitely in cases of constrictive pericarditis. The most transient changes are observed in rheumatic pericarditis; in this type the changes may disappear within a few days unless constrictive pericarditis develops. In uremic pericarditis, the electrocardiographic changes are permanent. In purulent pericarditis, normalization of the tracing coincides with healing of the form, while persistence of the changes indicates constrictive evolution. Irritation of the pericardium due to hemorrhage causes changes which disappear after elimination or adsorption of the effusion. According to the author, complete evolution of the electrocardiographic changes, from the upward RS-T displacement to the inversion of the T wave in all leads, rarely is observed.

The author feels that neither myocardial anoxemia nor myocardial lesions explain the electrocardiographic alterations. These are due to irritation of the epicardium followed by bioelectric changes.

This extremely valuable monograph presents the protocols and documents of selected interesting cases and certainly will be quoted extensively in the future.

A. LUISADA, M.D.

LA PRESSION DE LA ARTERIA PULMONAR. By V. A. J. Alberti, M.D. Buenos Aires, 1948, El Ateneo, 170 pages and 40 figures.

A detailed study is made of the various experimental devices by which pulmonary artery pressure can be measured in animals. This is followed by several chapters discussing the effects

5. Calcification of the ascending aorta is a valuable aid in the differential diagnosis of the etiology of aortic insufficiency and in distinguishing aneurysms from neoplasms.

The authors wish to thank Mr. Lloyd Matlovsky for the technical work in preparing the illustrations.

ADDENDUM

Since this paper was submitted for publication, the study of Leighton (*Radiology* 51:257, 1948) has appeared. Of eighteen cases of syphilitic aortitis, proved at autopsy, nine (50 per cent) showed calcification of the ascending aorta. Of thirty-seven clinical cases of syphilitic aortitis studied, seventeen (43 per cent) showed calcification of the ascending aorta.

REFERENCES

1. Cowdry, E. V.: *Arteriosclerosis*, New York, 1941, The Macmillan Company, p. 253.
2. Boyd, William: *Pathology of Internal Diseases*, Philadelphia, 1944, Lea & Febiger, pp. 90 and 103.
3. Bell, E. T.: *Textbook of Pathology*, Philadelphia, 1947, Lea & Febiger, pp. 203-206.
4. Mallory, T., and Schatzki, R.: Cabot Case, *New England J. Med.* 327:24, 1942.
5. Anitschkow, N. H.: Cited by Ophels, W. in Cowdry, E. V.: *Arteriosclerosis*, New York, 1941, The Macmillan Company, p. 257.
6. Christian, H. A.: *Pathology of Syphilis of the Aorta*, Oxford Monographs on Diagnosis and Treatment, Vol. 3, New York, 1940, Oxford University Press, p. 318.
7. Forbus, W. D.: *Reactions to Injury*, Baltimore, 1943, Williams & Wilkins Company, p. 682.
8. Bland, E., and Mallory, T.: Cabot Case, *New England J. Med.* 235:661, 1946.
9. Sproul, J.: Status and Clinical Application of Roentgenology of the Thoracic Aorta, *Am. J. Roentgenol.* 28:37, 1932.
10. Schwedel, J. B.: *Clinical Roentgenology of the Heart*, New York, 1946, Paul B. Hoeber, Inc., pp. 199 and 369.
11. Roessler, H.: *Clinical Roentgenology of the Cardiovascular System*, Springfield, Ill., 1943, Charles C Thomas, Publisher, p. 314.
12. Jackman, J., and Lubert, M.: The Significance of Calcification of the Ascending Aorta, *Am. J. Roentgenol.* 53:432, 1945.
13. Griffith, G. C.: The Early Diagnosis of Syphilitic Aortitis, *Am. Pract.* 2:299, 1948.
14. Thorner, M. C., and Carter, R. A.: The Roentgenologic Diagnosis of Syphilitic Cardiovascular Disease, *Am. Pract.* 2:301, 1948.
15. Maynard, E. P., Jr.: The Present Status of the Diagnosis of Uncomplicated Syphilitic Aortitis, *Bull. New York Acad. Med.* 18:383, 1942.
16. Woodruff, I. O.: Cardiovascular Syphilis, *Am. J. Med.* 4:248, 1948.
17. Allen, E. V., Barker, N. W., and Hines, E. H., Jr.: *Peripheral Vascular Diseases*, Philadelphia, 1946, W. B. Saunders Company, p. 511.

BIOMICROSCOPY OF CONJUNCTIVAL VESSELS IN HYPERTENSION

A CAPILLARY "HYPERTENSION PATTERN" AND THE OCCURRENCE OF INTRAVASCULAR CLUMPING (SLUGGED BLOOD) ARE DESCRIBED

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THE role played by capillaries in the hypertension disease process has not been generally emphasized and consequently has received inadequate clinical study and definition. Perhaps one explanation for the failure to evaluate completely the entire vascular tree in hypertension lies in the fact that the investigator has been limited by cumbersome, inadequate methods and an all too frequent lack of appreciation of the importance of the capillary in vascular physiology. From the morphologic approach pathologists have generally failed to recognize variations from normality in hypertension. As a result, the area of vascular pathology associated with hypertension has been rather sharply limited to the more striking arteriolar involvement. It is our purpose to evaluate capillary as well as arteriolar pathology in clinical assays of hypertension.

The older methods of nail-bed capillaroscopy have fallen into disuse because they failed to provide adequate definition of the peripheral vascular components. An excellent review of these techniques for capillary loop visualization was presented by Roth¹ in 1946. The origin of the capillary microscope was attributed to Lombard,² 1912, who first visualized the nail-fold capillaries in man. With magnifications up to 75 times, capillaries at the bases of both the finger and toenails were described as distinct comma-shaped loops. In 1917, Weiss and Müller³ first reported the clinical application of the method and took photomicrographs of the fields visualized. They described the presence of definite deformities and related them to disease entities. In acute nephritis the authors described a generalized widening and an increased number of capillaries, in Raynaud's disease marked irregularities were present, and in arteriosclerosis the capillaries were found to be longer and more tortuous than normal.

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Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Read at the Twenty-first Scientific Sessions of the American Heart Association, Chicago, Ill., June 19, 1948.

In 1922, Boas,⁴ using the Lombard technique, described the nail-fold capillaries in hypertension. From a study based on an undisclosed number of cases, this author concluded "the most that we can say is that in diseases in which the vascular system is affected the capillaries tend to change in appearance, and that this change manifests itself chiefly in an increase in length and tortuosity of the vessels." He also pointed out the difficulties in visualizing capillary flow but described a definite rapid flow in essential hypertension. Brown⁵ (1922), using the same method described marked capillary changes in fifty cases of cardiovascular renal disease. The most constant findings were a contracted type of capillary, frequent invisibility of the arterial limb, and marked disturbance in flow. In some areas capillaries appeared elongated and looped. The changes in flow were described as "halting and jerky" and at times isolated capillaries would disappear from view. There are, according to Brown, "essential differences in the capillaries of chronic nephritis and arteriosclerosis with or without hypertension." However, "in patients with malignant hypertension the morphologic and functional changes were most marked."

In 1924, Grzechowiak⁶ found changes in the capillaries in hypertension characterized by a beaded type of blood flow and varieties of shapes of loops during the active illness with a return to normal upon the subsidence of symptoms.

Other investigators utilizing the same Lombard technique with various slight improvements failed to confirm the presence of consistent morphologic or functional changes in the peripheral capillary bed in hypertension. Notable among these studies was that reported in 1932 by Mufson,⁷ who could not identify such irregularities as Grzechowiak had described. It is interesting to note that Mufson, while concentrating primarily on capillary pressure changes in hypertension, described a frequent narrowing, especially at the arteriole end, and a normal or more rapid flow of blood. Consistent with these findings were those of normal or increased capillary pressure in hypertension.

In an extensive report, Wright and Duryee⁸ in 1933 completely failed to confirm the previous reports of capillary changes associated with hypertension *per se*.

The importance of capillaries in the complete vascular network was being emphasized during this same period. The classical investigations of Cannon⁹ on the role of capillary stasis in shock appeared in 1918. Dale¹⁰ described the "paradoxical reaction" of histamine, which increased the tone of arterial muscle but produced a fall in blood pressure on intravenous injection. The explanation for this paradox was found in the capillaries where paralysis, dilatation, and stasis resulted from histamine stimulation. These studies together with the extensive investigations concerning normal capillaries by Krogh¹¹ and his students (1922-1929) served to establish a sound base line of essential principles and facts.

In 1921 Zeller¹² reported observations on the conjunctival vessels, using a corneal microscope with magnifications of 64 times. He observed normal blood flow and described intravascular as well as capillary abnormalities in arteriosclerosis, syphilis, and diabetes. Miliary aneurysms and cork-screw-type tortuosities were described. Small hemorrhages, passive venous congestion, and variations in flow rates were noted. His series did not include observations on hypertension.

Utilizing recent advances contributed by studies of living circulation in animals (Krogh,¹¹ Landis,¹³ Knisely,¹⁴ Lack¹⁵), an adaptation of basic techniques has proved useful and easily applicable to the clinical patient.

METHOD

The conjunctival vessels overlying the sclera of the eye were observed by reflecting bright parallel beams of light off the sclera. The images of the conjunctival vascular tree were studied by direct microscopy (Fig. 1). An ophthalmological slit lamp apparatus provided support for the patient's head and a maneuverable light source. A compound microscope was mounted on a horizontal rack

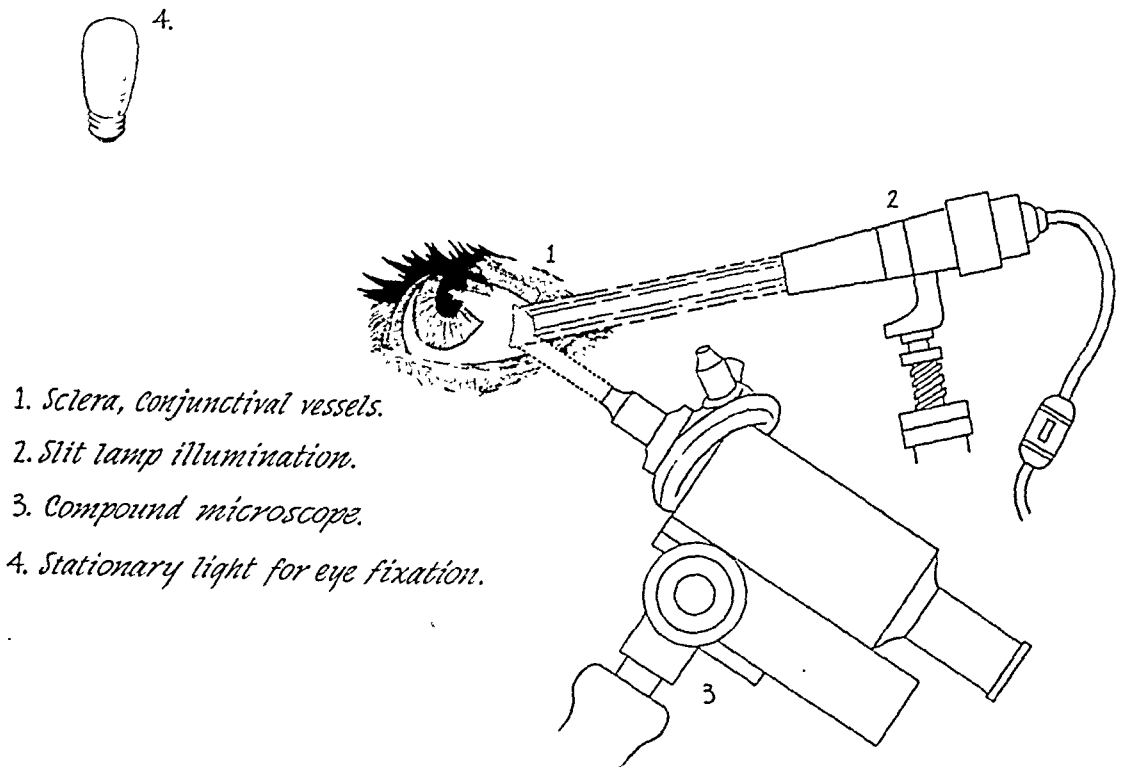


Fig. 1.—Diagram of apparatus for biomicroscopy of bulbar conjunctiva. The compound microscope (3) was replaced by a stereoscopic dissection microscope for survey studies.

and pinion; 16 and 24 mm. objectives provided safe working distances (Fig. 2, A and B). Wide-field oculars, 3 × to 20 ×, gave sufficient definition and magnification for these studies. Most observations were made with a 16 mm. apochromatic objective (for use without coverglass) and 5 or 10 × wide-field oculars. As much of the white of the eye as possible was exposed by the patient's fixation on a strategically placed small, red light in a darkened examination room. This technique was used for both compound and stereoscope microscopy. A wide-field stereoscopic dissecting microscope (Spencer) mounted on a side arm was used alternately with the rebuilt compound microscope described. The stereoscopic microscope was excellent for survey work and intravascular studies. Complete arteriovenous patterns with capillary networks were clearly visualized.

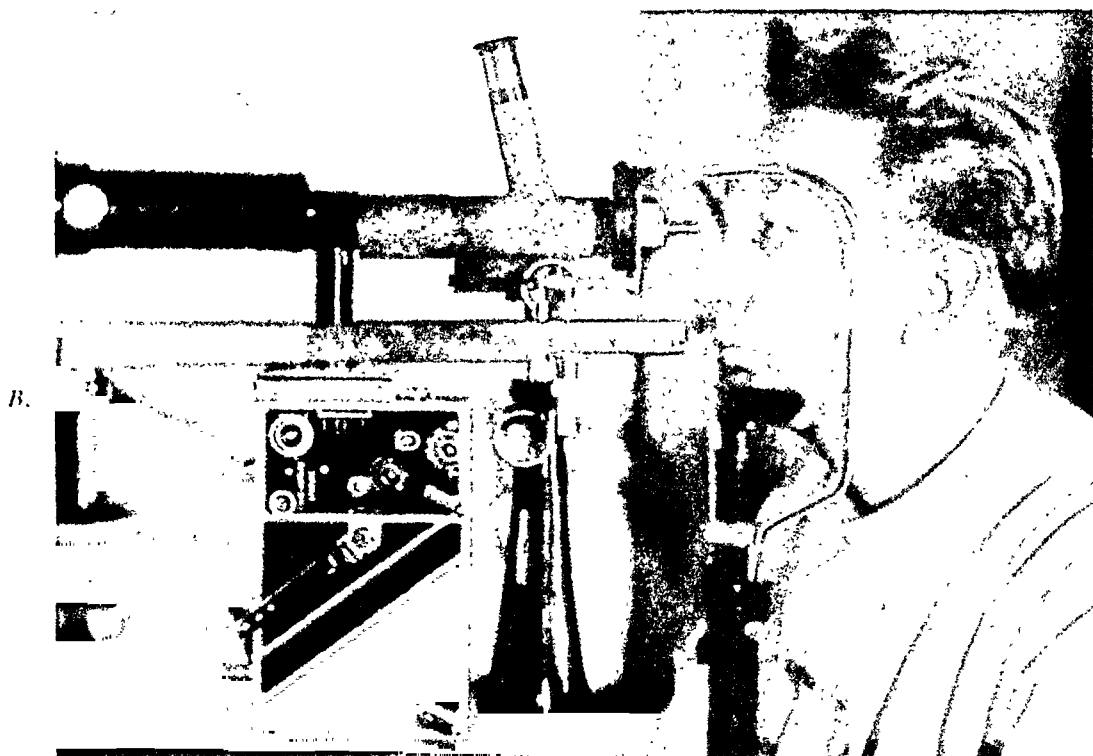
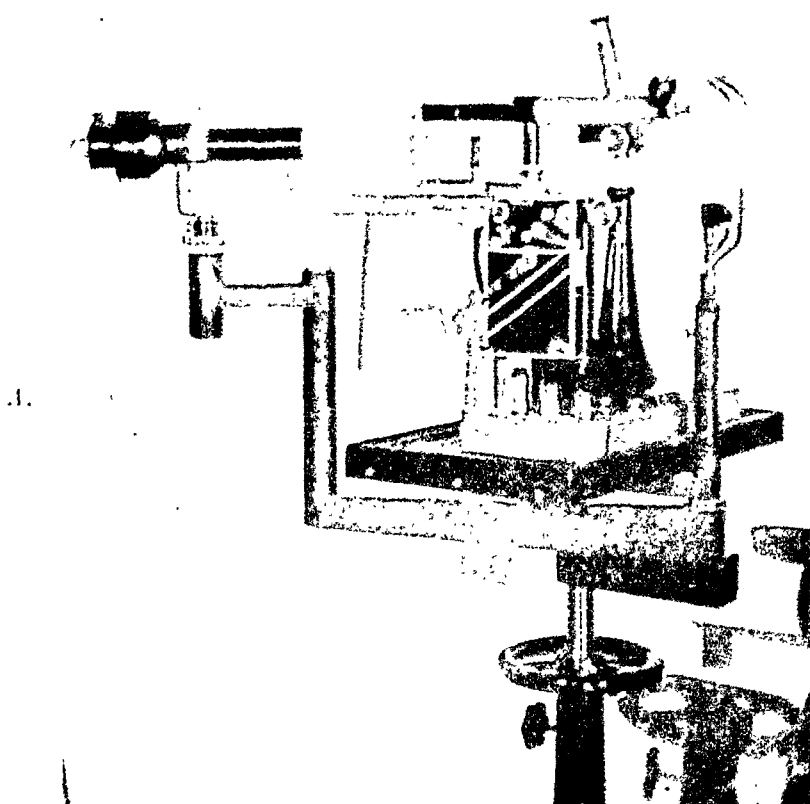


Fig. 2—A. Photograph of apparatus showing slide and mirror mechanism of camera.
 B. Photograph of apparatus with subject in position. Slide moving together
 of the retina was adequate for positive test.

Repeated examinations of patients made it possible to study changes in the peripheral vessels. Permanent records were obtained by Kodachrome cinematography, drawings from which are presented. The present apparatus is adapted for cinematography with an Eastman 16 mm. Ciné-Kodak Special Camera, mounted on the microscope by a side arm ocular. This ocular permits simultaneous recording and direct observation for continuous focusing.

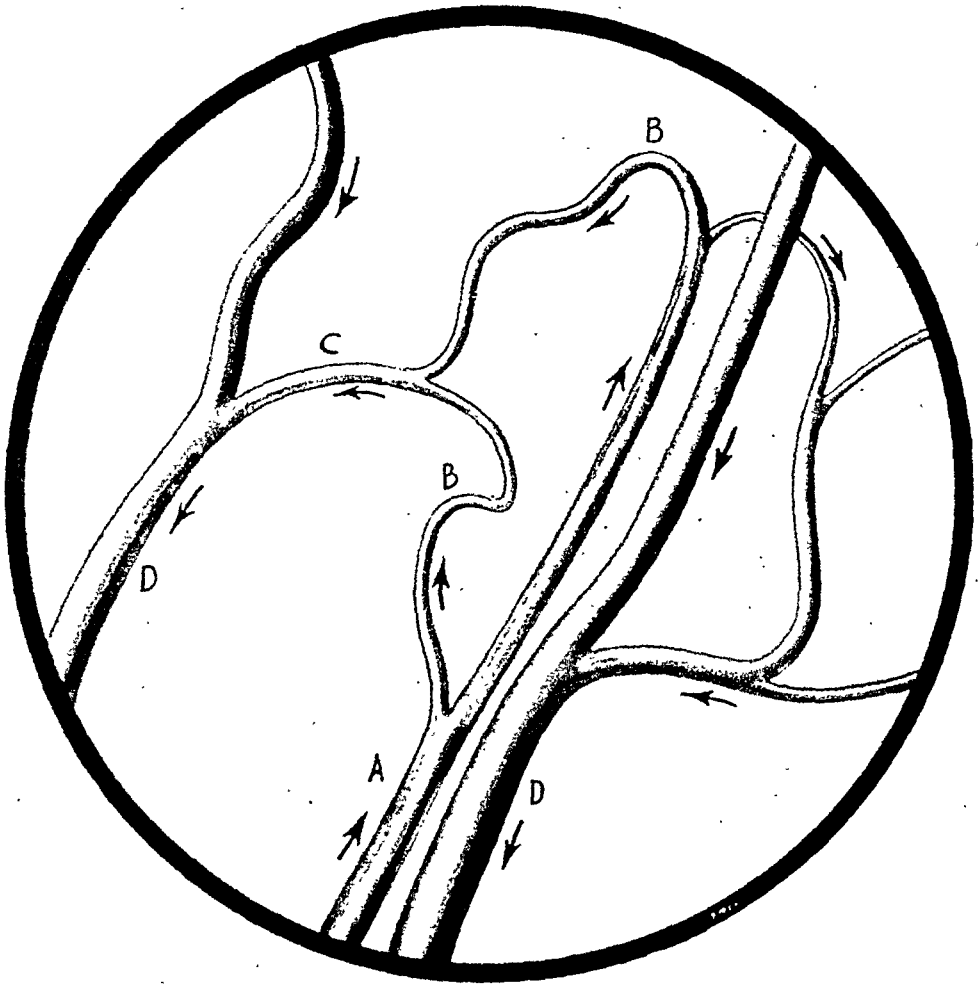


Fig 3.—Normal capillary pattern of conjunctiva. Arteriole and capillaries are uniform with smooth parallel walls. A, arteriole; B, capillaries; C, venule; D, collecting vein. Approximately $\times 100$ (on film).

RESULTS

Normotensive Subjects.—Two control series were concurrently studied. One, a hospital group of sixty-four normotensive patients, and, two, a group of fifty normal adults. Fig. 3 presents the structural plan of a typical normotensive subject (R.J.). The arterioles divide into numerous side capillaries and terminate with an end capillary. The latter, on occasion, functions as a “through and through” channel. The capillaries appear to be of uniform caliber throughout with a smooth, winding course and no evidence of sacculations or abnormal points of constriction. The capillary of the bulbar conjunctiva has indefinite

subdivisions of postarterial, midloop, and prevenule segments. Only rare arterio-venous anastomoses of the short type are seen. There are individual variations in venous patterns with frequent tortuosities, varying with individuals and being correlated in some degree with the age of the patient. Flow rates in normal individuals are not remarkable and are consistent with the physiology of a given area. With magnifications of one hundred times or more, it is possible to trace the course of an individual red cell through the entire capillary loop.

The morphologic changes in the two control series will be briefly summarized. Of the sixty-four nonhypertensive hospital patients, capillary changes were absent in forty-six (72 per cent) and present in eighteen (28 per cent). The changes noted were only minimal. No patients revealed abnormalities of the hypertension pattern, but showed, on the other hand, various changes such as abnormal dilatations, minimal narrowing, spiderweb branches, and a rare focal nodularity. In the fifty normal adults of the control series the capillaries were normal in appearance in all instances. Capillary distensibility was present throughout and there was no evidence of thickening of the capillary wall.

Hypertensive Subjects.—A series of one hundred hypertension patients with blood pressures of 150/100 or more were evaluated by biomicroscopy. Definite capillary irregularities were present in ninety-eight of the patients. These have been roughly evaluated as being of minimal involvement in 9 per cent, moderate in 57 per cent, and marked in 34 per cent. These changes were morphologic, consisting of generalized narrowing of the capillary lumen, elongation with angular tortuosities, abnormal loopings, focal constrictions, and occasional sacculations.

Definite angularities (that is, fixed turns of roughly 30 degrees or more), and an increased length of over-all capillary segment with abnormal loopings were consistent findings. Accompanying such morphologic changes was increased thickness of capillary wall which showed some degree of thickening in 83 per cent. In striking correlation with the morphologic irregularities was the loss of normal capillary distensibility in 89 per cent.

Marked sparseness of the capillary bed was found in cases of long-standing hypertension. The typical capillary findings in hypertension are shown (Fig. 4) in a drawing copied from a 16 mm. Kodachrome moving picture of the patient. The elongation of individual capillaries with a tendency to looping of the mid-capillary segment appeared as a striking early change. The thick-walled capillaries seen in hypertension have a tubular appearance, and fixed tortuosities are striking. The loss of normal distensibility was easily noted when large intra-vascular red cell clumps and thrombi could be followed through capillary channels. Such findings were sufficiently striking and consistent to suggest a hypertension pattern of capillary pathology as represented diagrammatically in Fig. 5.

The capillary changes of the "hypertension type" and the height of the diastolic pressures showed a definite correlation. With increasing diastolic pressures there was a greater incidence of marked capillary change. In the two patients in whom capillary findings were absent the diastolic pressures occurred in the 100 to 119 mm. group; both of these patients had histories of early hypertension.

The age distribution curve reveals a wide sampling with predominance of patients in the middle age groups. There was no correlation between the age of an individual patient and the degree of capillary changes of the hypertension type described.

Sex distribution of this hypertension series bears no significant relationship to the degree of capillary pathology observed.

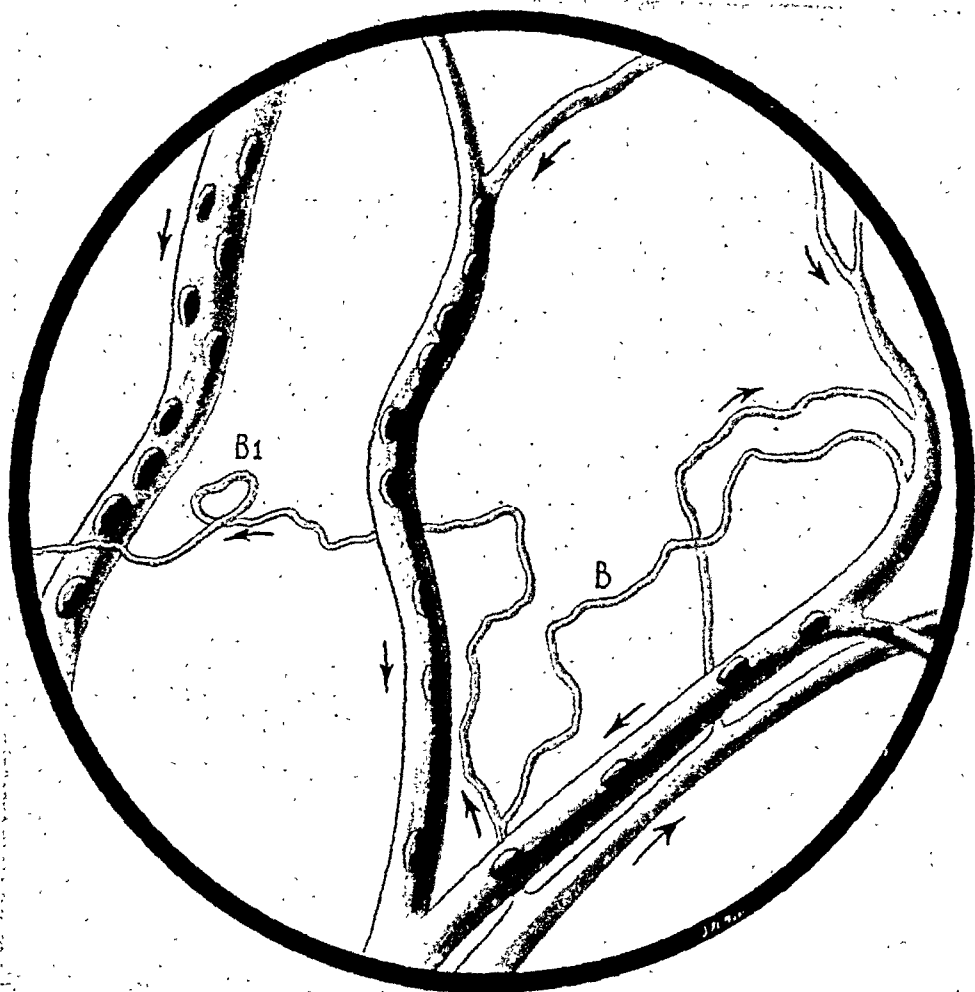


Fig. 4.—Capillaries of conjunctiva in hypertension. Traced from 16 mm. Kodachrome film of patient. Note elongated, narrowed capillaries (B) with marked tortuosities and sharp, fixed angular turns. Capillary loop shown (B¹). Approximately $\times 100$ (on film).

The evaluation of arterioles in the hypertension patients revealed definite irregularities in 80 per cent, with an entirely normal arteriolar structure present in 10 per cent. There was no evaluation made in the remaining 10 per cent.

INTRAVASCULAR AGGLUTINATION PHENOMENON OR "SLUGGED BLOOD"

The fact that intravascular pathology of considerable severity involving clumped masses of red cells and/or clumped masses of white blood cells may be present in numerous disease states has been reported by several early investigators. In 1908, Cropper¹⁶ described the intravascular clumping of infected red

cells in a fatal case of pernicious malaria. He suggested that such formations might form embolisms, thromboses, or infarctions in various organs. Iwai and Meisai,¹⁷ 1925, reported the formation of agglutinated masses of red cells in Raynaud's disease. At their invitation Hayano, using a Zeiss corneal microscope, observed changes in the flow of conjunctival vessels. Broken columns of blood flow in capillaries were described after bathing with cold water and it was felt that these could be due to the formation of small, intravascular blood clots.

CAPILLARY "HYPERTENSION" PATTERN

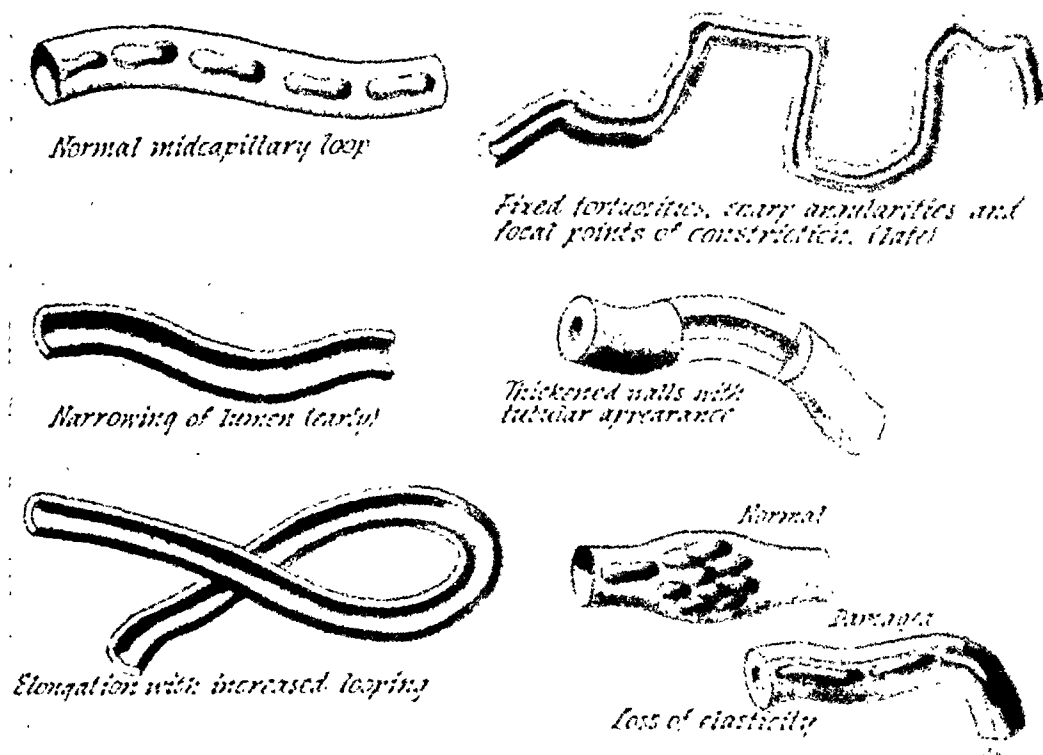


Fig. 5—Hypertension pattern of capillary changes as seen with the biomicroscope (diagrammatic). The significant morphologic changes in conjunctival vessels were confirmed by histopathologic study of necropsy material.

Histologically, intravascular agglutinated masses of red cells in malaria were demonstrated in various tissues at autopsy by Dudgeon and Clarke¹⁸ in 1917. Thromboses were particularly prominent in the adrenals, brain, and kidneys. They pointed out that this observation of agglutinated erythrocytes in malaria leads not only to the occlusion of capillaries but to obstruction of arterioles as well.

This phenomenon consists primarily of intravascular clumpings of red cells forming large, agglutinated, firm masses inconsistent with shell layer type of normal vascular flow. It appeared to us that such intravascular changes were interesting but definitely nonspecific. Although these changes were of un-

doubted importance in vascular pathology, it was not within the province of this paper to embark upon a study of this abnormality. However, we noted that intravascular agglutinations of some severity were present in many of our subjects. These changes were graded roughly on a basis of size, number, and toughness of clumps (Fig. 6). Grade 1 represented fine granularities of several erythrocytes which are rather uniform and not too upsetting to flow rates; Grade 2 indicated definite clumping which tends to hold together in larger collecting veins; Grade 3 indicated large agglutinations which completely block out normal flow; and Grade 4 represented almost complete clumping of erythrocytes, which suggests the appearance of "sludge."

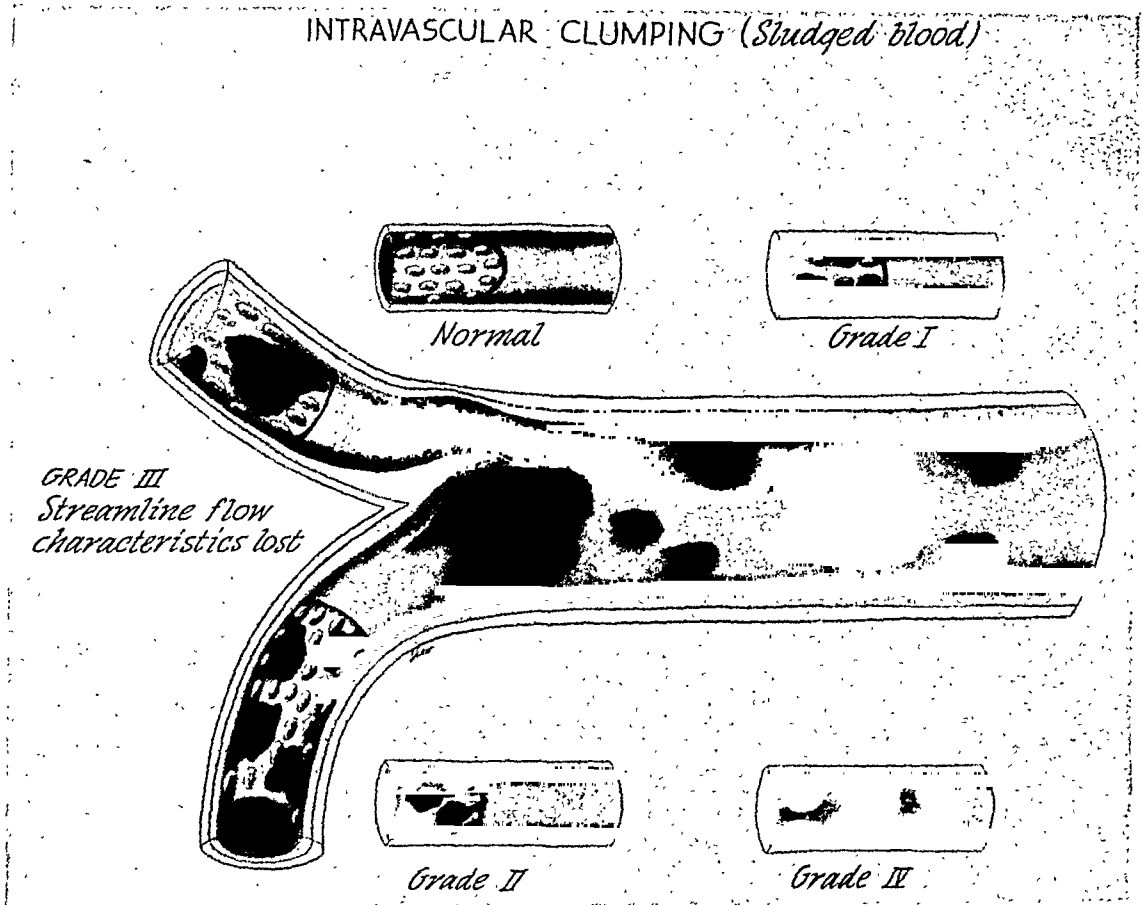


Fig. 6.—Grading of severity of intravascular red cell clumpings or sludged blood. The clinical significance of these various grades has not yet been established.

Of our series of hypertension patients, intravascular agglutinations of erythrocytes were absent in only four. Subjective estimations revealed 50 per cent with Grade 1 clumping, 45 per cent with Grade 2, 4 per cent with Grade 3, and 1 per cent with Grade 4 clumping. A sharp line of demarcation occurred in the hypertension series between Grades 2 and 3, with 95 per cent having involvement in Grades 1 and 2 indicative of minimal to moderate severity. There was no relation of degree of clumping to blood pressure levels. Transient capillary and venous thromboses were present in 73 per cent of the hypertension series.

Of the sixty-four nonhypertensive hospital control patients, intravascular agglutinations were present in forty-three, with fourteen in Grade 1, twenty-three in Grade 2, five in Grade 3, and one in Grade 4. Of the fifty normal adult control subjects, only one showed intravascular pathology (Grade 1). It was of interest to note that the presence of granularities in this one subject may be related to the fact that this individual was recuperating from an upper respiratory infection.

DISCUSSION

The original premise for studying patients by direct visualization of the conjunctival vessels was directed toward analyses of intravascular pathology similar to the recently described "sludged blood" by Knisely and co-workers¹⁹ at the University of Chicago and the University of Tennessee. The intravascular clumping of red cells is an important physical phenomenon and is definitely inconsistent with "streamlined" hemodynamics. Altered cell nutrition as a result of inadequate flow characteristics and the formation of thromboses and infarctions subsequent to such intravascular clumping may all be of considerable significance in the explanation of numerous disease manifestations. However, the nonspecificity of this phenomenon immediately became apparent and its relation to any given disease process required additional clarification and definition of basic factors involved. On the other hand, the adaptability of this technique toward an analysis of the morphologic pathology of the peripheral vascular tree in various disease states, and hypertension in particular, soon became evident.

An advantage of the method presented lies in the fact that the wall of individual capillaries can be discerned with proper illumination and magnification. The clear images obtained contrast sharply with the older methods and make possible more critical analyses of peripheral vascular pathology.

The consistent changes in capillaries associated with hypertension indicate that the area of peripheral vascular resistance includes capillaries as well as arterioles. On occasion, significant findings in hypertension have been confined to the capillaries. The arterioles of the conjunctiva showed no changes in these cases. If this peripheral area were indicative of general systemic involvement, it would suggest that peripheral resistance could be initiated by capillaries in some cases. Similar capillary pathology in hypertension was reported in the central nervous system by Scheinker,²⁰ in 1948. He demonstrated at necropsy that vascular alterations in early arterial hypertension were confined mostly to capillaries with evidence of proliferative and degenerative changes. Such changes in capillaries may be correlated with a general vascular deterioration, and progressive atresia of individual capillaries might well occur.

SUMMARY AND CONCLUSIONS

1. A new method of biomicroscopy of conjunctival vessels, utilizing high magnification (up to 200 times), is presented.
2. The results from a study of one hundred cases of hypertension suggest a "hypertension pattern" of capillary pathology. This pattern is characterized

by extensive narrowing, elongation, and looping of capillaries, which, in addition, show fixed angularities or tortuosities, tubular thickening of walls, and loss of normal distensibility. Ninety-eight per cent of all hypertensive patients showed significant capillary changes of this type.

3. The severity of this capillary hypertension pattern correlates directly with the rise in diastolic pressure.

4. No significant correlations of capillary vascular damage with sex or age could be determined.

5. Arteriolar pathology is noted in 80 per cent of the hypertension series.

6. Nonhypertensive hospital patients, who composed a control series, showed no capillary involvement in 72 per cent. Minimal changes of bizarre types were present in 28 per cent; none showed the "hypertension pattern" of capillary pathology.

7. Intravascular clumping of red cells was noted in 96 per cent of the hypertension series and in 67 per cent of the control series.

8. The findings of this study indicate that it may be worth while clinically to evaluate the role of the capillary in hypertension by this method and to direct efforts toward a systemic evaluation of the pathology of the capillary tree as it relates to the hypertension process.

REFERENCES

1. Allen, E. V., Barker, N. W., and Hines, E. A.: *Peripheral Vascular Diseases*, Chapter V, *Naifold Capillaries in Man*, by Roth, Grace M., Philadelphia, 1946, W. B. Saunders Company, p. 148.
2. Lombard, W. P.: Blood Pressure in the Arterioles, Capillaries and Small Veins, *Am. J. Physiol.* **29**:335, 1912.
3. Weiss, E., and Müller, O.: Ueber Beobachtung der Hautkapillaren und ihre klinische Bedeutung, *München. med. Wchnschr.* **1**:609, 1917.
4. Boas, E. P.: The Role of the Capillaries in Circulatory Disorders, *Med. Clin. North America*, **5**:1007, 1922.
5. Brown, G. E.: Capillary Observations in Cardiovascular Renal Disease, *Ann. Clin. Med.* **1**:69, 1922.
6. Grzechowiak, F.: Der Kapillardruck, besonders während der Schwangerschaft, *Ztschr. f. Geburtsh u. Gynäk.* **87**:128, 1924.
7. Mufson, J.: A Study of Capillary Pressure in Nephritis and Hypertension, *Am. J. M. Sc.* **183**:632, 1932.
8. Wright, I. S., and Duryce, A. W.: Human Capillaries in Health and in Disease, *Arch. Int. Med.* **52**:545, 1933.
9. Cannon, W. B.: Blood in Shock and Hemorrhage, *J. A. M. A.* **70**:526, 1918.
10. Dale, H. H.: Histamine Shock, *J. Physiol.* **52**:355, 1918.
11. Krogh, A.: *The Anatomy and Physiology of Capillaries*, New Haven, 1922, Yale University Press.
12. Zeller, C.: Studies on the Conjunctival Vessels, *Klin. Monatsbl. f. Ophthal.* **66**:609, 1921.
13. Landis, E. M.: Micro-injection Studies of Capillary Blood Pressure in Human Skin, *Heart*, **15**:209, 1930.
14. Knisely, M. H.: An Improved Fused Quartz Living Tissue Illuminator, *Anat. Rec.* **71**:503, 1938.
15. Lack, A. R.: The Occurrence of Intravascular Agglutinations in Avian Malaria, *Science* **96**:520, 1942.
16. Cropper, J.: Phenomenal Abundance of Parasites in the Peripheral Circulation of a Fatal Case of Pernicious Malaria, *J. Trop. Med.* **2**:91, 1908.
17. Iwai, S., and Meisai, N.: Etiology of Raynaud's Disease, *Japan M. World*, **5**:345, 1925.
18. Dudgeon, L. S., and Clarke, C.: A Contribution to the Microscopical Histology of Malaria, *Lancet*, **2**:153, 1917.
19. Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L.: Sludged Blood, *Science*, **106**:431, 1947.
20. Scheinker, I. M.: Alterations of Cerebral Capillaries in the Early Stages of Arterial Hypertension, *Am. J. Path.* **24**:211, 1948.

THE NORMAL UNIPOLAR PRECORDIAL AND LIMB LEAD ELECTROCARDIOGRAM

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THE increasing recognition of the diagnostic value of unipolar precordial and limb leads has given a tremendous impetus to electrocardiography. A number of publications have described various phases of unipolar precordial electrocardiography and the evaluation of patterns such as those seen in myocardial infarction, bundle branch block, and ventricular hypertrophy.¹⁻¹¹ However, statistical data on the normal electrocardiogram as obtained by unipolar extremity and precordial leads are extremely scant. The publication to which most authors refer is that of Kossmann and Johnston,¹² but the data of these authors are based on only thirty cases, in which V_6 was not used. Since their paper in 1935, other articles limited to certain phases of the normal precordial electrocardiogram have appeared, such as data for children¹³ and the intrinsic deflection.¹⁴ It was, therefore, felt desirable to study a larger group of normal individuals of various ages, in an attempt to establish more definitely the normal variations. Since this study was completed, two publications on unipolar leads in normal subjects have appeared.¹⁵⁻¹⁶

Wilson and his co-workers¹ demonstrated in a series of papers that precordial leads may, for practical purposes, be considered semidirect leads from the heart. These workers showed that a close relationship exists between the electrocardiographic pattern obtained from the epicardium of the right ventricle and that obtained from the right precordium, and that a similar relationship exists between patterns obtained from the left ventricle and the left precordium. The value of multiple, as compared to single, precordial leads was stressed by the observation that a precordial or an epicardial electrode largely reflects the potential variations of the myocardium directly under the electrode, and that the effects of distant ventricular areas vary inversely as the cube of the distance.¹ In using multiple precordial leads, the use of an indifferent electrode with potential as near zero as possible is to be preferred. Wilson and his group demonstrated that their central terminal was nearly zero, having a potential of approximately 0.3 millivolt. This is in contrast to the CF leads when the left leg lead may be far from indifferent, especially in vertical hearts.

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Aided in part by a grant from the Mrs. Albert E. Schwabacher Fund.

Furthermore, the recording of unipolar extremity leads requires the use of the central terminal. Goldberger¹⁷ has modified Wilson's technique for taking the unipolar extremity leads, and records "augmented" potentials which are 50 per cent greater than those obtained by the Wilson method. Unipolar precordial leads and unipolar augmented extremity leads have therefore become widely used in electrocardiography.

Since the original work of Lewis,¹⁸ the importance of the intrinsic deflection has been stressed by Wilson and his associates¹ and by Sodi-Pallares and his associates.¹⁴ The time of onset of the beginning of the final downstroke of the QRS complex in relation to the time of onset of the beginning of the QRS complex is said to indicate the time required for the passage of the impulse to the epicardium underlying the exploring electrode. As such, the time of onset of the intrinsic deflection (the ventricular activation time) will be delayed in conditions that increase the mass of myocardium (hypertrophy) or delay the passage of the impulse (bundle branch block or myocardial infarction).

THE ELECTROCARDIOGRAPHIC POSITION OF THE HEART

Wilson and associates¹ have emphasized the importance of the electrocardiographic position of the heart in explaining variations in the electrical axis and patterns in the standard limb leads. These authors have noted that despite similar precordial patterns, some individuals show strikingly different patterns in their standard limb leads and may show left axis deviation, right axis deviation, or no axis deviation. They demonstrated that this variation in the standard leads can be explained by the electrocardiographic position of the heart and its relation to the extremities. The position of the heart may be determined by a comparison of the potential variations of the left arm and left leg leads with those of V_1 and V_6 in the precordial leads. Depending on whether the potential of the left ventricle (V_5 or V_6) is transmitted to the left arm or left leg, Wilson and associates have classified their cases as horizontal or vertical, respectively, referring to the electrocardiographic rather than to the anatomic position of the heart.

SUBJECTS AND METHODS

All the subjects on which the present data are based have had complete physical examinations and six-meter roentgenographic studies of the heart, and, as far as could be determined, were free of cardiovascular disease. None had cardiovascular symptoms or a disease known to affect the heart, such as disease of the thyroid, anemia, rheumatic fever, and so forth. Many were medical students and members of the house staff. Those composing the group in the third to seventh decades were obtained from flying personnel of the United Air Lines,* whose physical examinations and requirements for performance are notably high; and from psychiatric patients in the Langley Porter Clinic* who were studied prior to electric shock treatment. None of

*The authors are indebted to Dr. A. C. Ladd, Medical Director, United Air Lines, South San Francisco, Calif., and the Staff at the Langley Porter Clinic, San Francisco, Calif., for their cooperation in this study.

the latter group had cardiovascular disease, as far as could be determined, and had been referred to the clinic solely for their psychiatric disorders. Miscellaneous individuals from all age groups for whom an electrocardiogram had been requested as part of a routine physical examination were included. These individuals had no signs or symptoms of cardiovascular disease. The small group of infants was obtained from the Well-Baby Clinic of the University of California Clinics. Prior to the final statistical evaluation, all the case histories were carefully rescrutinized and any questionably normal subjects were excluded.

One hundred fifty individuals remained, and these were studied with standard limb leads, unipolar precordial leads, and unipolar leads of the left arm (aV_L), right arm (aV_R), and left leg (aV_F). Goldberger's modification of Wilson's¹⁷ method was used. A minimum of six unipolar precordial leads were taken on each case, V_1 to V_6 , according to the recommendations of the American Heart Association. The tracings were carefully analyzed and work-sheets were made out recording the amplitude and duration of each significant electrocardiographic variable. In addition, the time of onset of the intrinsic deflection in relation to the onset of the QRS (the ventricular activation time), the electrocardiographic position of the heart, the R/S and R/T ratios, as well as other ratios and factors of voltage were studied.

The age range of the subjects was as follows:

1 to 9 years.....	5
10 to 19 years.....	4
20 to 29 years.....	49
30 to 39 years.....	45
40 to 49 years.....	30
50 to 59 years.....	12
60 years or more.....	5
	<hr/>
	150

RESULTS

The Normal Electrocardiogram.—Table I summarizes the findings in our total series of 150 subjects and includes the total normal group and separate data for those individuals among the normal group who had left or right axis deviation. These data for voltage of the unipolar extremity leads must be decreased by 50 per cent if a direct comparison with the results of Kossmann and Johnston is desired (see above). For example, the mean R wave in V_L in Kossmann and Johnston's¹² data is 1.13 mm.; in our data the corresponding figure for aV_L is 2.1 millimeters.

Electrocardiographic Position of the Heart.—Table II tabulates the electrocardiographic position of the heart obtained in our normal subjects. It was found that there was a direct relationship between left axis deviation in the

TABLE I. THE VENTRICULAR DEFLECTIONS IN THE UNIPOLAR LIMB AND PRECORDIAL LEADS IN NORMAL SUBJECTS
(MEASUREMENTS IN MILLIMETERS)

LEAD	NORMAL (150 CASES)				NORMAL—LEFT AXIS DEVIATION (21 CASES)				NORMAL—RIGHT AXIS DEVIATION (19 CASES)			
	MEAN	± ST. DEV.	MIN.	MAX.	MEAN	± ST. DEV.	MIN.	MAX.	MEAN	± ST. DEV.	MIN.	MAX.
V ₁ Q R S T ID	0	0	(0)	(0 7.0)	0	0	(0 0)	(0 4.5)	0	0	(0 0)	(0 7.0)
	2.3	1.5	(0 2.0)	(0 25.0)	1.8	1.3	(0 3.5)	(0 18.0)	2.1	1.6	(0 1.5)	(0 17.0)
	8.6	4.3	(-0.4)	(-0.4 +4.0)	8.0	3.7	(-2.5)	(-2.5 +3.0)	8.4	4.3	(-1.5)	(-1.5 +3.0)
	0.15	1.58	(0 0)	(0 0.03)	-0.4	1.32	(0 0)	(0 0.02)	+0.26	1.06	(0 0)	(0 0.03)
	0.02	0.007			0.02	0.006			0.02	0.008		
V ₂ Q R S T ID	0	0	(0 0)	(0 16.0)	0	0	(0 2.0)	(0 12.0)	0	0	(0 0)	(0 0)
	5.9	3.1	(0 0)	(0 29.0)	5.0	2.9	(0 4.0)	(0 18.0)	5.9	2.8	(0 2.0)	(0 11.0)
	12.7	5.3	(-3.0)	(-3.0 +18.0)	10.3	4.8	(-2.5)	(-2.5 +9.0)	15.4	5.0	(4.0)	(4.0 29.0)
	5.52	3.32	(0 0)	(0 0.04)	4.08	2.68	(0.01)	(0.01 0.035)	4.6	2.34	(+1.5)	(+1.5 +11.0)
	0.025	0.006			0.03	0.006			0.024	0.008	(0.015)	(0.015 0.04)
V ₃ Q R S T ID	0.01	0.06	(0 0)	(0 0.5)	0	0	(0 0)	(0 0)	0	0	(0 0)	(0 0)
	8.9	4.3	(1.5)	(1.5 26.0)	8.6	4.0	(4 4)	(4 17.0)	7.4	2.6	(3.0)	(3.0 13.0)
	8.8	5.3	(0 0)	(0 25.0)	7.5	4.3	(3 3)	(3 16.0)	11.3	5.7	(2.0)	(2.0 25.0)
	5.38	2.96	(-2.0)	(-2.0 +16.0)	4.67	4.37	(-0.1)	(-0.1 +13.0)	5.18	2.21	(+2.0)	(+2.0 +10.0)
	0.03	0.007	(0.02)	(0.02 0.04)	0.03	0.005	(0.02)	(0.02 0.04)	0.029	0.007	(0.015)	(0.015 0.04)
V ₄ Q R S T ID	0.1	0.4	(0 0)	(0 3.0)	0.05	0.16	(0 0)	(0 0.5)	0.03	0.02	(0 0)	(0 0.5)
	14.2	5.5	(4.0)	(4.0 27.0)	12.5	5.0	(5.0)	(5.0 27.0)	13.4	4.4	(4.0)	(4.0 23.0)
	5.2	4.0	(0 0)	(0 20.0)	4.3	3.2	(0 0)	(0 13.0)	6.5	5.0	(0 0)	(0 19.0)
	4.8	2.76	(0 0)	(0 +17.0)	4.2	2.67	(-0.1)	(-0.1 +13.0)	4.18	1.79	(+1.0)	(+1.0 +8.0)
	0.034	0.007	(0.02)	(0.02 0.05)	0.04	0.007	(0.03)	(0.03 0.045)	0.032	0.007	(0.020)	(0.020 0.04)

V ₆	Q	0.3	0.6	(0	(0	0.4	(0	0.2	0.1	(0	(0	1.0
	R	12.1	4.4	(-4.0	(3.0	5.4	(6.0	10.2	3.7	(4.0	(4.0	20.0
	S	1.5	1.5	(0	(24.0	1.1	(0	2.0	1.8	(0	(0	6.0
	T	3.43	1.62	(0	(6.0	1.66	(+1.0	3.29	1.49	(+2.0	(+2.0	+8.0
	ID	0.04	0.01	(0	(+9.0	0.007	(0.025	0.033	0.008	(0.02	(0.02	0.04
V ₆	Q	0.4	0.5	(0	(2.0	0.4	(0	0.3	0.2	(0	(0	2.0
	R	9.2	3.6	(-4.0	(22.0	4.1	(-4.0	8.1	3.6	(2.5	(2.5	16.0
	S	0.6	1.0	(0	(7.0	0.5	(0	0.8	0.9	(0	(0	3.5
	T	2.43	1.11	(-0.5	(+5.0	1.18	(+0.5	2.37	1.01	(+1.5	(+1.5	+5.0
	ID	0.04	0.01	(0.02	(0.05	0.01	(0.03	0.03	0.01	(0.02	(0.02	0.05
V _L	Q	0.2	0.5	(0	(3.5	0.4	(0	0.1	0.2	(0	(0	3.5
	R	2.1	2.1	(0	(10.0	2.5	(0.5	0.9	0.8	(0	(0	3.0
	S	0.4	3.9	(0	(18.0	0.7	(0	0.5	3.6	(0	(0	18.0
	T	0.53	1.26	(-4.0	(+6.0	0.81	(-1.0	0.45	1.0	(2.0	(2.0	+2.0
V _R	Q	2.0	3.7	(0	(8.0	2.6	(0	1.8	2.7	(0	(0	8.0
	R	0.8	0.9	(0	(5.0	0.6	(0	0.8	0.8	(0	(0	3.5
	S	4.3	4.0	(0	(13.0	0.9	(0	4.3	4.6	(0	(0	13.0
	T	-2.31	0.92	(-5.0	(+1.5	0.67	(-3.0	-2.08	0.84	(-4.0	(-4.0	-1.0
V _F	Q	0.5	1.4	(0	(3.0	1.0	(0	0.7	0.2	(0	(0	2.0
	R	1.3	8.3	(0	(20.0	2.2	(0	10.5	4.2	(0.7	(0.7	20.0
	S	0.2	1.3	(0	(8.0	1.4	(0	0.4	2.1	(0	(0	2.0
	T	1.86	1.1	(-0.5	(+5.0	0.92	(-0.5	1.84	0.96	(+0.5	(+0.5	+4.0

1.0 = time of onset of the intrinsic deflection or ventricular activation time.

standard leads and horizontal hearts and between right axis deviation and vertical hearts. Records with no axis deviation were intermediate in position (Fig. 1). It was apparent from Table II that the majority of the normal subjects had vertical or semivertical hearts from an electrocardiographic (not anatomic) standpoint.

TABLE II. THE ELECTROCARDIOGRAPHIC POSITION OF THE HEART AS OBTAINED IN 150 NORMAL SUBJECTS

Horizontal.....	3
Semihorizontal.....	11
Intermediate.....	28
Semivertical.....	68
Vertical.....	40
	<hr/> 150

Of the fourteen subjects with semihorizontal or horizontal hearts, only two were under the age of 39. This is of some significance, because unless gross obesity or an elevated diaphragm was present (such as occurs in late pregnancy), horizontal hearts were not seen in normal individuals before the fourth decade. The prediction of the electrocardiographic position of the heart from the build of the patient was fairly reliable in slender individuals (who usually had vertical hearts), but one was often surprised to find vertical or intermediate hearts in individuals who were sthenic in appearance and definitely overweight (Fig. 2A). In order to determine the effects of position of the heart and axis deviation on the unipolar patterns, data were obtained from nineteen normal subjects whose electrical axes were $+80^\circ$ or more (obtained by the method of Carter and his associates¹⁹) and from twenty-one normal individuals whose electrical axes were $+10^\circ$ or less (Table I).

The tables and Fig. 1 illustrate that although the precordial leads were essentially similar, the unipolar limb Leads aV_L and aV_F differed in the group with left axis deviation from those in the group with right axis deviation. Lead aV_R was similar in both groups, because in this lead the exploring electrode on the right arm faced the orifices of the great vessels and the cavities of the heart and hence was essentially negative throughout the QRS interval. Since the changes in the unipolar extremity leads were so obviously related to the position of the heart, whereas the precordial leads were much less influenced by the position of the heart, greater reliance must be placed on the precordial leads for electrocardiographic diagnosis. Unusual rotation may explain a variety of so-called atypical electrocardiographic patterns (see Discussion).

The P Wave.—The shape, amplitude, and duration of the P wave did not differ from that noted by previous authors in the standard leads. Almost invariably the P wave was inverted in Lead aV_R , often was inverted in aV_L , and usually was upright in aV_F . The P wave was small and diphasic in a small percentage of normal subjects in V_1 , but the broad, negative diphasic quality noted by Hecht²⁰ in mitral stenosis, and characteristic of auricular enlargement, was not seen. The P wave was usually small and upright or isoelectric in the remaining precordial leads, very rarely diphasic in the left precordial leads.

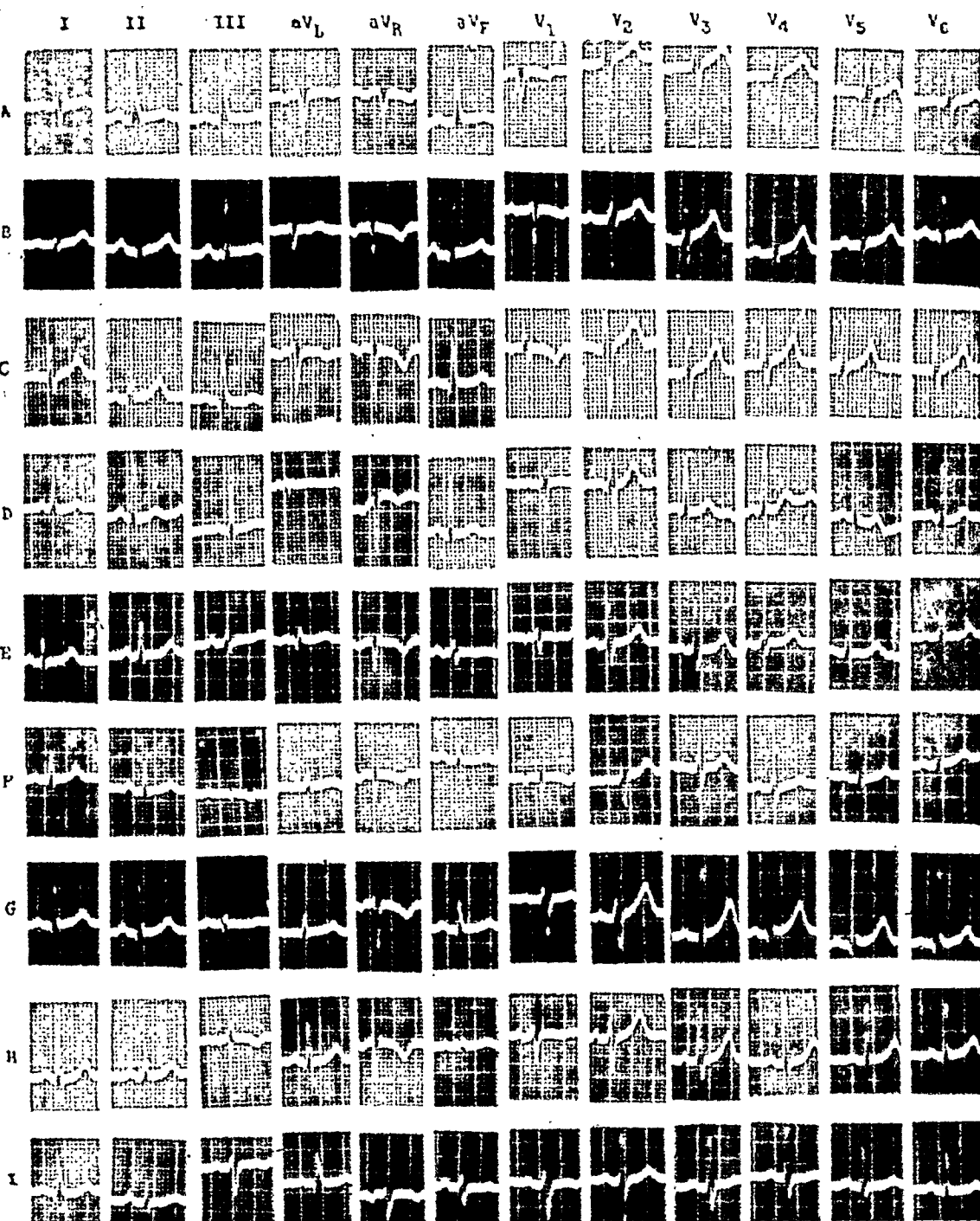


Fig. 1.—Unipolar leads in nine normal subjects arranged in order from the most vertical to the most horizontal positions of the heart.

The QRS Complex.—Fig. 1 illustrates the reciprocal relationship between the R and S waves as the exploring electrode was moved across the precordium from right to left (V_1 to V_6). The R wave usually was small in Leads V_1 , V_2 , and V_3 ; became larger in V_4 ; and obtained its maximum height in either Lead V_4 or V_5 , after which it tapered off in V_6 and V_7 . The S wave showed a reciprocal decrease, although the decrease in size was more gradual and the change to the left of the transitional zone was not so marked as occurred occasionally with the R wave. The R/S ratio was calculated, and the increase was striking as one moved from the right to the left precordium (Table IIIA).

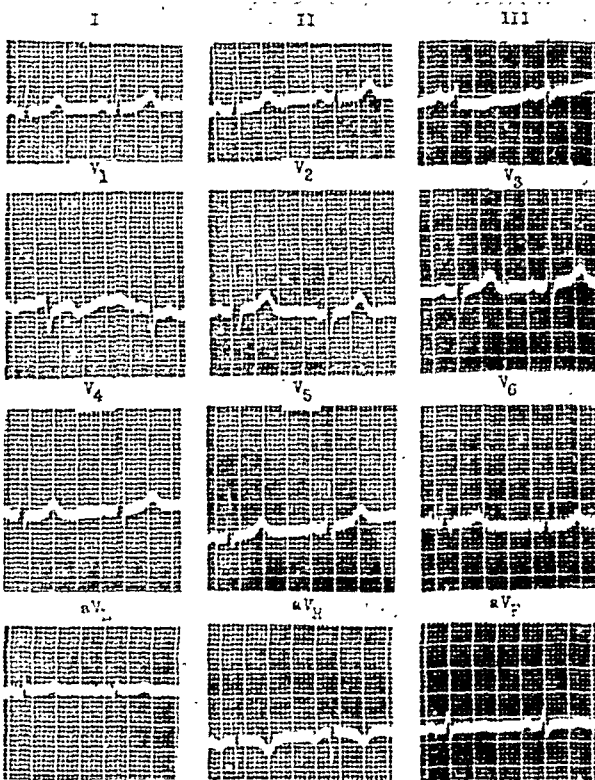


Fig. 2A.

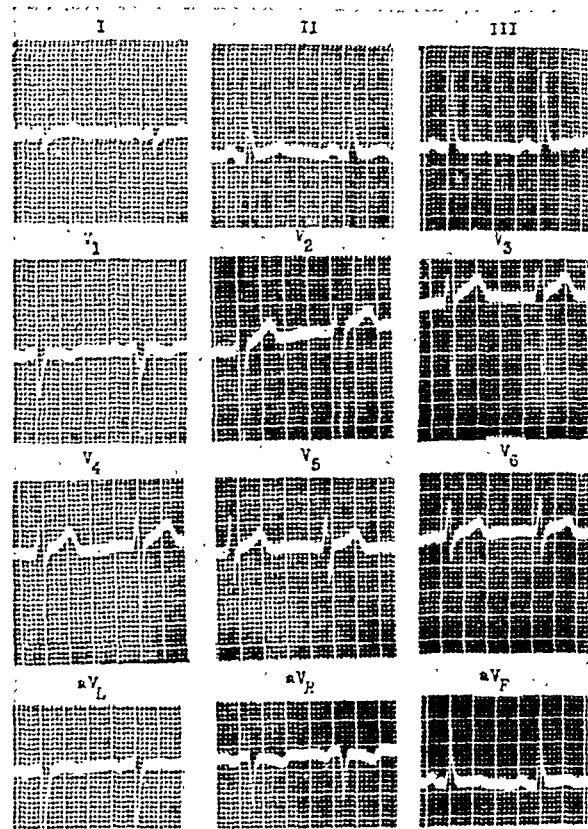


Fig. 2B.

Fig. 2 A.—A. R., woman, age 48. Obese; 159 pounds, 5 feet 3 inches. Transitional zone between precordial Positions 1 and 2. Note Q wave in aV_L with small total QRS complex.

Fig. 2 B.—A. M., man, age 25. Vertical position, axis $+105$ degrees. Note the relatively low T in aV_R and the inverted T in aV_L . Transitional zone between Positions 5 and 6.

The maximum figure for the R/S ratio in Lead V_1 in the adults was 1.0 and the minimum figure in Lead V_5 was 1.0. The ratio obtained by dividing the R/S ratio in V_5 by the R/S ratio in V_1 $\left(\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1} \right)$ is noted in Table IIIB.

The transitional zone denoting the change in potential over the right and left ventricles usually occurred in Lead V_3 or V_4 , but occasionally was seen in V_2 or V_5 and rarely in V_6 or V_7 (Figs. 2A and 2B). Notching and slurring of the QRS complex was not uncommon in the complexes obtained from the transitional zone; this was considered to be due to an overlapping of the effects of both ventricles, a normal phenomenon.

TABLE III, A. THE RATIO OF THE R WAVE TO THE S WAVE (R/S RATIO) IN THE PRECORDIAL LEADS OF NORMAL ADULT SUBJECTS

LEAD	MEAN	±ST. DEV.	MIN.	MAX.
V ₁	0.3	0.3	(0	1.0)
V ₂	0.2	1.2	(0.1	13.0)
V ₃	1.4	1.4	(0.1	10.0)
V ₄	4.1	3.8	(0.2	19.0)
V ₅	7.3	4.7	(1.0	24.0)
V ₆	9.0	5.0	(2.3	22.0)

TABLE III, B. THE DATA OBTAINED BY DIVIDING THE R/S RATIO IN V₆ BY THE R/S RATIO IN V₁ ($\frac{R/S \text{ IN } V_6}{R/S \text{ IN } V_1}$) IN NORMAL SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
$\frac{R/S \text{ in } V_6}{R/S \text{ in } V_1}$	32.0	26.9	(3.6	100)

Voltage of the QRS Complex.—Because of the abnormalities found in the R/S ratio in Leads V₁ and V₅ in ventricular hypertrophy,^{9,10} particular attention was paid to the voltage of the various waves of the QRS complex, and the data obtained are summarized in Table I. Data for children are incomplete in view of the frequent presence of high voltage of the QRS complex in normal children. The R/S ratio as obtained from leads over the right and left precordium reflects the relative effects of the right and left ventricles. In addition to the individual voltage of the waves, the total voltage of the left and right ventricular potentials was determined. The sum of R in V₁ and S in V₅ was considered to reflect the total right ventricular potentials; the sum of R in V₅ and S in V₁, the left ventricular potentials. These data were important in providing base-line figures for the diagnosis of ventricular hypertrophy.^{9,10} Tables IV and V summarize the findings of these R and S relationships as obtained in Leads V₁ to V₆, in adults (over the age of 20).

TABLE IV. THE SUM OF THE AMPLITUDES OF THE R WAVE IN V₁ AND OF THE S WAVE IN V₅ IN NORMAL ADULT SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
R in V ₁ + S in V ₅	3.7	2.39	(0	10.5)

TABLE V. THE SUM OF THE AMPLITUDES OF THE S WAVE IN V₁ AND OF THE R WAVE IN V₅ IN NORMAL ADULT SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
S in V ₁ + R in V ₅	19.9	5.6	(6	35)

The Q Wave.—No theoretical discussion of the production of waves will be attempted except to state that normally Q waves in the precordial leads were found only in QRS complexes reflecting left ventricular potentials.

Q waves were never seen in Lead V_1 or V_2 , and rarely in Lead V_3 , although a QS complex may occasionally be seen normally in Leads V_1 and V_2 (Fig. 1). Q waves were commonly seen in Leads V_4 to V_6 , but were small, usually 1.0 to 2.0 mm. or less, and less than 0.04 second in duration. Q waves were occasionally seen in Lead V_3 when the transitional zone was displaced to the right and prominent R waves were present in V_3 . In children and young adults, the Q waves in the left ventricular leads occasionally were as deep as 3.0 to 4.0 mm., but when this figure was obtained, the R wave was correspondingly taller. The maximum percentages of the Q/R ratio are summarized in Table VI, since by means of this ratio the Q waves may be quantitated more satisfactorily. When the amplitude of the QRS complex was 6.0 mm. or more, the Q/R ratio was less than 25 per cent. However, when the total QRS deflection was small, that is, 4.0 to 6.0 mm., then the Q/R ratio was occasionally greater than 25 per cent in our normal subjects (see aV_L in Fig. 2A). Q waves occurring with small QRS complexes, therefore, should be interpreted with caution.

TABLE VI. THE RATIO OF THE Q WAVE TO THE R WAVE (Q/R RATIO) IN NORMAL SUBJECTS

LEAD	MEAN	± ST. DEV.	MIN.	MAX.
V_1	0	0	(0)
V_2	0	0	(0)
V_3	0.025	0.002	(0	0.03)
V_4	0.04	0.032	(0	0.1)
V_5	0.07	0.039	(0	0.16)
V_6	0.087	0.043	(0	0.21)
aV_L	0.238	0.165	(0	0.75)
aV_R	4.97	2.96	(0	14.0)
aV_F	0.1	0.06	(0	0.28)

Q waves were also seen in normal subjects in the unipolar extremity leads. The deepest and most consistent were seen in Lead aV_R . In this lead the QRS complex was found to be negative throughout most of the duration of depolarization, usually being characterized by a QS complex. Frequently, however, a small R or R' wave was seen either before or after the negative deflection (Figs. 2A, 4B, and 5). In the latter instance, the downward deflection of the QRS complex was a deep Q wave. The R wave rarely exceeded 3.0 mm. in aV_R ; the maximum height of the R wave in aV_R was 5.0 millimeters.

The Q wave in Lead aV_F was similar to that found in V_5 or V_6 , and reflected the transmission of the left ventricular potential to the left leg in vertical hearts. It usually was small, less than 25 per cent of the R wave. When the QRS complex is of small amplitude, the Q wave in Lead aV_F (just as is true in aV_L) may occupy a greater per cent of the R wave. These data are important as a base line for comparison with the findings in posterior myocardial

infarction. Occasionally, a QS complex was found in Lead aV_F in normal subjects with horizontal hearts, in association with a QS complex in Lead V_1 . The RS-T segment and T wave were normal when a QS complex was present.

The Q wave in Lead aV_L was more difficult to evaluate, particularly when the Q and R waves were equal in size. Experience has indicated the importance of Q waves in Lead aV_L in the diagnosis of myocardial infarction, and Rosenbaum and his associates²¹ have described their value in the diagnosis of

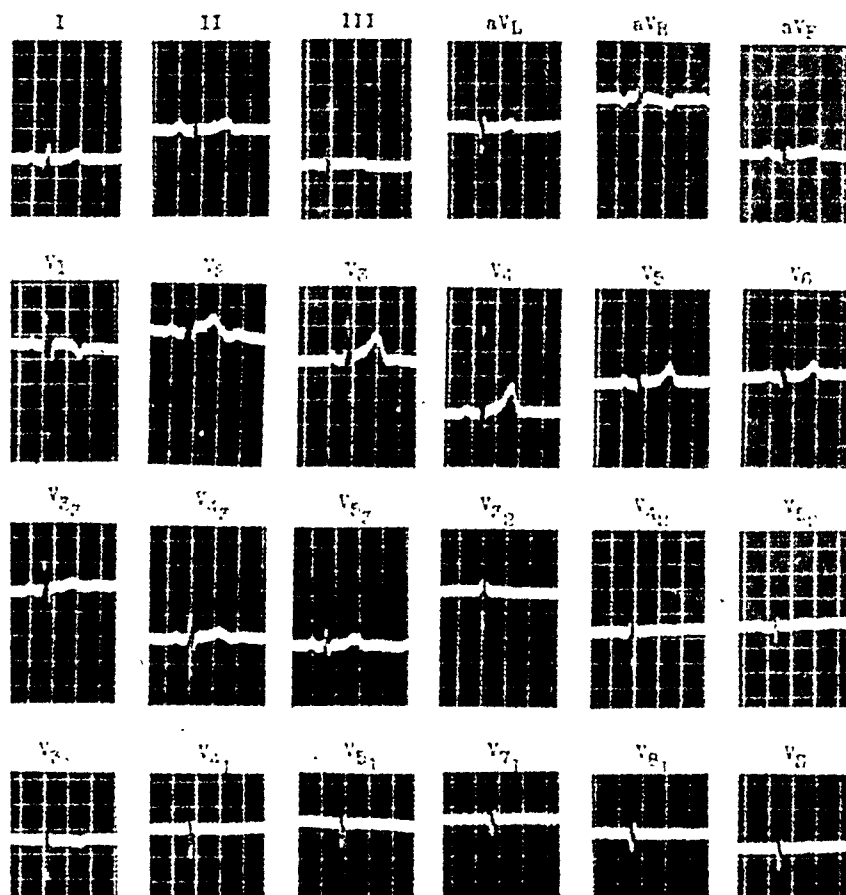


Fig. 3.—S. M., girl, age 9, U152854. Note the deep narrow Q wave with small R in aV_L , V_1 to V_3 in the first intercostal space (labelled V_1 to V_3), the left shoulder (V_8), and at V_3 in the second intercostal space (indicated in fig. by V_{3_2}). Note that a small initial R is present in the fourth position in both the first and second intercostal spaces (indicated in fig. by V_{4_1} , V_{4_2}).

high lateral lesions. Therefore, it was considered extremely important to define the normal range of this wave. Usually the Q wave in Lead aV_L was small, both absolutely and in proportion to the R wave (Tables I and VI). On infrequent occasions, however, the amplitude of the Q wave equalled or exceeded that of the R wave in aV_L . In some cases it was difficult to determine whether or not a minute R wave preceded the negative deflection in Lead aV_L (Fig. 1,E). This was particularly true in vertical and semivertical hearts

with total voltage of the QRS complex in Lead aV_L less than 5.0 or 6.0 mm. (Figs. 3 and 4A); QS waves in Lead aV_L were also seen occasionally in subjects with vertical hearts, although commonly the pattern consisted of a small R and deeper S wave (Figs. 2B and 4B). Rarely, a deep, narrow Q wave with a minute R wave may be found in aV_L (Fig. 3). In these cases leads over the left lateral chest below the clavicle may show variably a small R and R' and a deep Q with a minute R wave (Fig. 3). Review of those cases with a QS complex in aV_L revealed that all were associated with vertical or semivertical hearts, and with a normal RS-T segment and T wave.

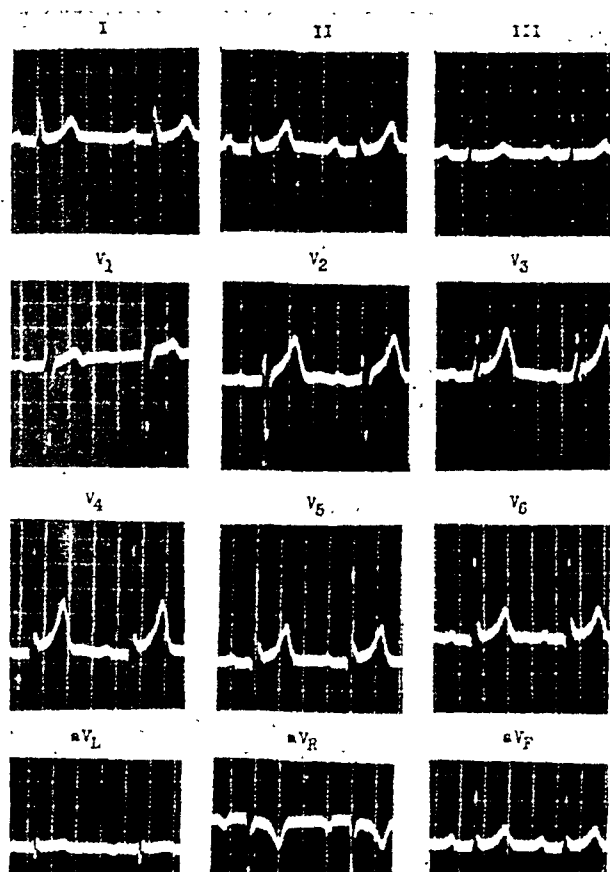


Fig. 4 A.—M. F., man, age 34. Semivertical heart with small initial and late R waves in aV_L . Note the elevated RS-T segments with their contour concave upward in the precordial leads.

In many of the normal subjects with prominent Q waves in the left arm lead, but with normal or absent Q waves in the left precordial leads (Figs. 1, E and 2A) exploratory leads were taken over the anterior precordium, in the second and third intercostal spaces, at Positions 4 to 7. This was done because of the occasional instance in which a high lateral myocardial infarction is manifested solely by a significant Q wave in the left arm lead.²¹ It was found that the only normal subjects with significant Q waves in Lead aV_L with normal or absent Q waves in the left precordial leads were those in whom a vertical

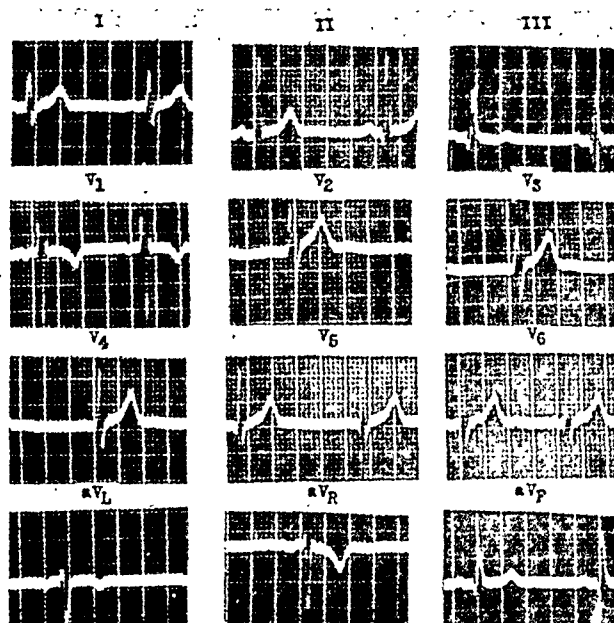


Fig. 4 B.—S. M., man, age 23. Obese; 152 pounds, 5 feet 4 inches. Vertical heart. Note the R' and the inversion of the T wave of 2.5 mm. in V_1 .

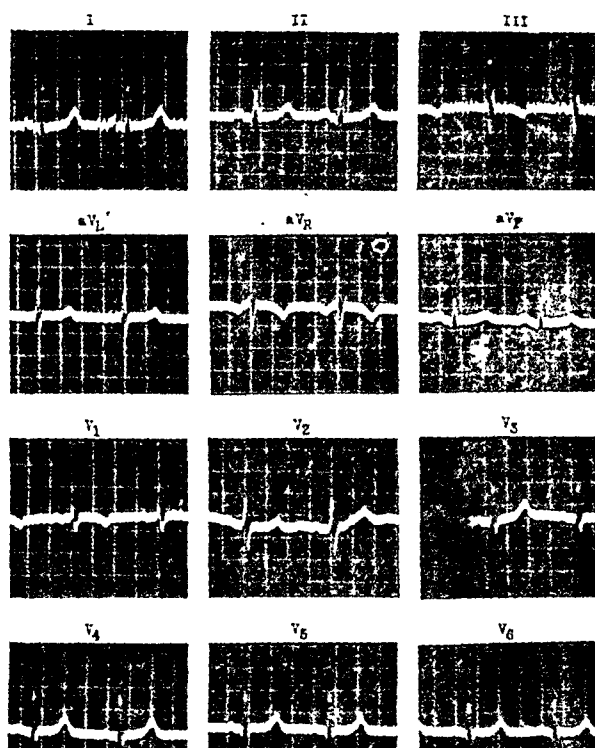


Fig. 4 C.—R. A., woman, age 58, U111922. Obese; 167 pounds, 5 feet. Intermediate heart. Note the deep Q in Lead III (5.0 mm., 55 per cent of tallest R wave in standard leads). Minute Q in aV_1 . The Q wave in Lead III is the result of the relative negativity of the left leg as compared to the left arm.

or intermediate position was present. Exploratory leads high over the anterior precordium did not reveal the findings characteristic of anterior myocardial infarction. In these patients, just above or just below the clavicle, or at the point of the shoulder, QRS complexes were obtained which resembled those of the left arm lead (Fig. 3). These complexes were interpreted as being the proximal extension of the positional variations noted in Lead aV_L . A study of the right arm lead in these cases revealed prominent Q waves and/or minute R or R' waves; these findings are consistent with a posterior rotation of the apex of the heart, so that both the right and left arm leads face the cavities of the ventricles.⁷

Intrinsic Deflection and Ventricular Activation Time.—The maximum ventricular activation time in our normal subjects was 0.035 second in Lead V_1 and 0.055 second in Leads V_5 and V_6 . In no normal subject was the ventricular activation time as much as 0.04 second in Lead V_1 or 0.06 second in Lead V_5 or V_6 . The time of onset of the intrinsic deflection was consistently greater in the left precordial leads than in the right precordial leads. This is clearly shown in Fig. 1, which demonstrates that the peak of the R wave occurs earlier in the QRS interval in leads from the right precordium than in leads from the left precordium. A separate study²² utilizing six simultaneous precordial leads confirmed the normal range and maximum data on ventricular activation time in normal subjects.

The RS-T Segment.—Elevation of the RS-T segment (up to 3.0 mm.) was not uncommon in Lead V_1 , V_2 , or V_3 , but rarely exceeded 1.0 mm. in Leads V_4 to V_6 (Fig. 4A). The contour in these instances was concave upward, with a rapid ascent, and in no case was the RS-T segment horizontal or convex upward so as to simulate the pattern seen in coronary disease. Depression of the RS-T segment was more rarely seen and was never greater than 0.5 millimeter. When the RS-T segment was depressed, the contour was similar to that seen when the segment was elevated, that is, concave upward. Apparently a depressed RS-T segment of minor degree is of greater significance than a similar change in the RS-T segment that is elevated.

T Waves.—Data on the T waves are summarized in Table I. The ratio of the R wave to the T wave in the corresponding lead was also obtained so as to have more quantitative information in regard to T waves (Table VII). Inversion of the T wave was common in Lead V_1 in normal subjects, infrequent in V_2 , rare in V_3 , and was never found in V_4 except in children. The maximum inversion of the T wave in V_1 was 2.5 mm. in adults. Furthermore, in the children studied (our findings in children agree essentially with those reported by Battro and Mendy¹¹) all had normal T waves in Leads V_5 and V_6 , with prominent R waves. In the cases in which inversion of the T wave was present in V_2 , V_3 , or V_4 , the leads to the right also had inverted T waves. An inverted T wave in any precordial lead with a normally upright T wave in the next position to the right was not found. The inverted T waves in Leads V_1 and V_2 were as a rule relatively small, the maximum being 2.5 mm. in adults (Figs. 2B, 4B, and 4C). The inverted T waves usually were associated with

a slightly convex and slightly depressed RS-T segment (Fig. 1). The R waves were small in the leads in which the T wave was normally inverted, the S wave was prominent, and no Q waves were visible; such complexes were clearly of right ventricular origin. Inverted T waves were not seen in the normal subjects when the QRS complex reflected left ventricular potentials. When the transitional zone was displaced to the left, the T wave occasionally was inverted in Leads V_2 and V_3 ; inspection of the R/S ratio clearly indicated the right ventricular origin of the complexes.

TABLE VII. THE RATIO OF THE R WAVE TO THE T WAVE (R/T RATIO) IN NORMAL SUBJECTS

LEAD	NO.	MEAN	ST. DEV.	MIN.	MAX.
V_1	59	1.4	0.9	(0.3	7)
V_2	145	1.4	1.4	(0.2	12)
V_3	150	1.9	1.6	(0.3	13)
V_4	150	3.1	2.3	(0.3	9)
V_5	150	3.5	1.6	(1.0	9)
V_6	150	4.1	1.9	(1.7	10)
aV_L	91	2.6	1.9	(0.1	10)
aV_F	142	4.6	3.2	(0.3	14)
aV_R		0	0	(0)

The maximum upright T wave in Lead V_1 was 4.0 millimeters. The tall T waves in Leads V_2 and V_3 that occasionally occur normally in these leads (Table I) must be kept in mind when tall T waves in the right precordial leads are being considered to support a diagnosis of posterior myocardial infarction. The T wave was frequently found to be inverted in the left arm lead in vertical hearts (Figs. 2B and 5). Table I defines the range of this wave in nineteen cases of right axis deviation with vertical hearts. It was found that the maximum inversion of the T wave in Lead aV_L , even in a normal vertical heart, was 2.5 mm. (Fig. 5). In no instance in which the R wave in Lead aV_L was 5.0 mm. or taller was the T wave inverted. All inverted T waves in aV_L seen in the normal vertical hearts occurred with small R waves and prominent S waves, or with QS complexes. When the height of the R wave was 3.0 to 4.0 mm., the T wave rarely was inverted more than 0.5 mm., and often was flat (Fig. 6). This was also true of the left leg lead. In no normal subject was the T wave in the left leg lead inverted when the R wave exceeded 5.0 mm. in height. Since the R wave in Lead aV_L was upright in subjects with horizontal hearts with left axis deviation, it should be noted that the T wave in aV_L was not inverted in any of the subjects with normal horizontal hearts (Figs. 1 and 7).

Transitional Zone.—As the precordial electrode was moved across the precordium from the right to the left, an intermediary zone was noted which varied from precordial Positions 2 to 6. Usually this transitional zone was demonstrated in Lead V_3 or V_4 . The transition was occasionally abrupt, so that ventricular complexes one position apart varied strikingly (Figs. 4A and 8), or was extended over several positions. To the right of the transitional zone, the ventricular complexes were clearly of right ventricular origin, with a small

R, prominent S, and absent Q wave. To the left of the transitional zone, the ventricular complexes were clearly of left ventricular origin and manifested a prominent R, small to absent S, and perhaps a small Q wave. When the transitional zone was displaced far to the left, Lead V_5 or V_6 showed complexes of right ventricular origin. In these cases, leads farther to the left, such as V_7 and V_8 , demonstrated the typical left ventricular potentials. This is of importance when right ventricular hypertrophy is being considered, because

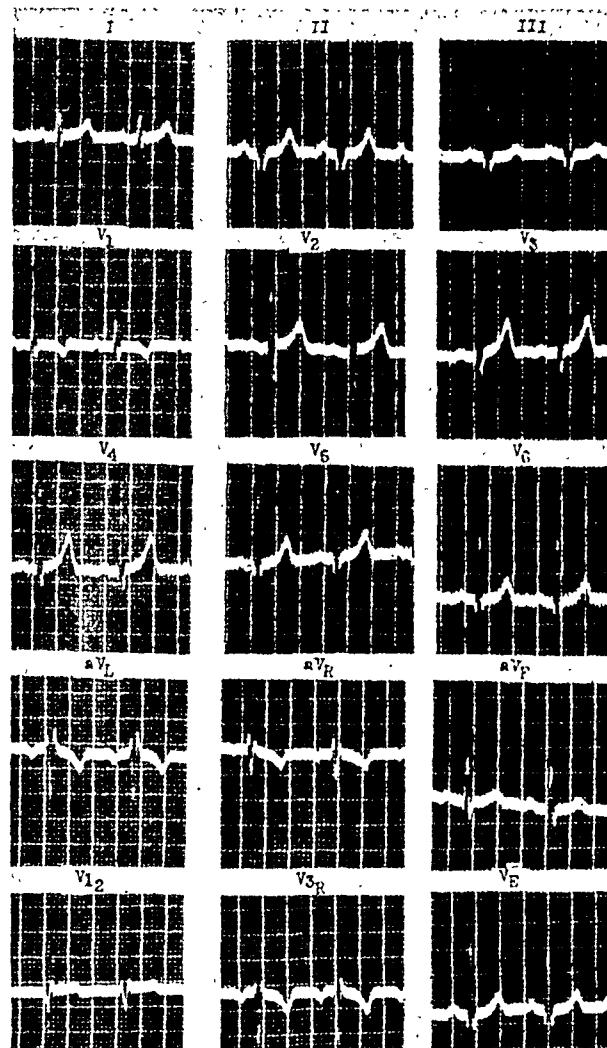


Fig. 5.—F. H., woman, age 35. Vertical heart with counterclockwise rotation of the heart and transitional zone between Positions 2 and 1. Leads over the right precordium (V_{3R} and V_1 in the second intercostal space marked V_{12}) are of right ventricular origin, while V_E (xiphoid) resembles V_6 .

characteristically in this condition a small R and prominent S wave occur in the left precordial leads. More rarely, when the transitional zone is displaced to the right, leads from precordial Position 2 may demonstrate left ventricular potentials and may also simulate right ventricular hypertrophy, in which prominent R waves occur over the right precordium. When the transitional zone was displaced to the right in our normal subjects, leads farther to the right

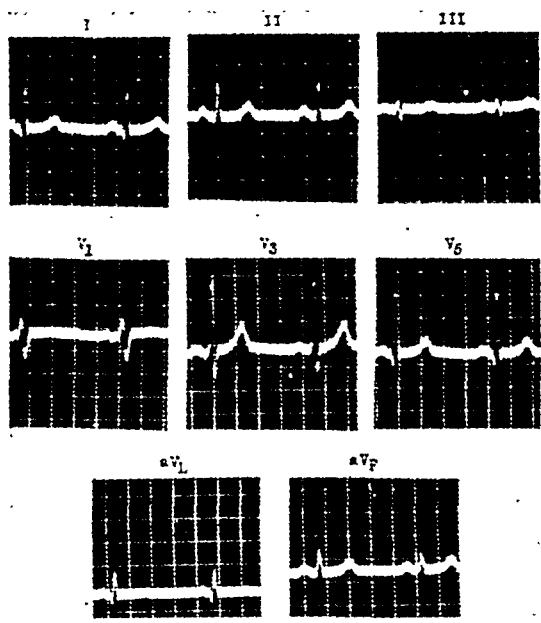


Fig. 6.—W. T., man, age 52. Normal heart confirmed by autopsy. Q wave 25 per cent of the R wave (1:4) in aV_L with flat T wave. Interpretation of Q and T waves in Lead aV_L should be cautious when the total voltage of the QRS complex is small.

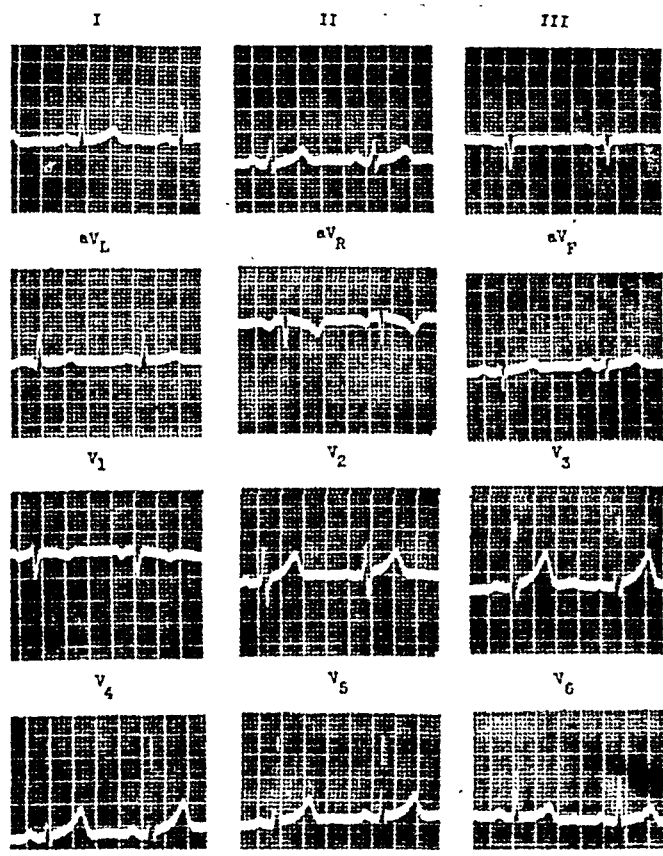


Fig. 7.—H. H., man, age 57, U78776. Horizontal heart, axis -20 degrees.

demonstrated the typical right ventricular potentials (Fig. 5). The form of the QRS complex in the transitional zone was occasionally bizarre, with variable R and S waves, often with slurred and notched QRS complexes. This type of transitional zone QRS complex was only rarely seen in more than one position.

Rotation of the Heart.—At times, in records obtained from normal subjects, unusual axis deviation, unusual position of the transitional zone, or the appearance of Q waves in the left arm lead suggested the possibility of unusual rotation of the heart. Posterior displacement of the apex has been already referred to in the discussion of the Q waves. Very infrequently, marked clockwise rotation of the heart on its longitudinal axis (viewed from the apex) was assumed in subjects in whom the transitional zone was displaced to the left. In these cases, the transitional zone was demonstrated in Lead V_6 ; left ventricular potentials were obtained over the right posterior thorax, from the right upper abdomen, and from the right lateral chest. Right ventricular potentials were obtained over precordial Positions 1 to 5, the ensiform process of the sternum, and high over the right anterior chest (Fig. 8). This transmission of potentials suggests that clockwise rotation of the heart was present, so that the potential changes of the left ventricle were noted over the left and right posterior chest and were transmitted anteriorly to the right upper abdomen and right lateral chest. Study of the unipolar extremity leads in relationship to the usual six precordial leads and exploratory leads over the precordium to the left and right were often helpful in demonstrating unusual rotation of the heart. The possibility of cardiac abnormality was always considered when bizarre rotation of the heart was encountered.

Unipolar Extremity Leads.—The pattern of the unipolar extremity Leads aV_L and aV_F depended upon the electrocardiographic position of the heart, and therefore upon the electrical axis of the heart. If the heart was horizontal and the axis shifted to the left, the normal pattern in Lead aV_L was similar to that seen in the left precordial leads (to the left of the transitional zone), and consisted of a prominent R wave, a small to absent S wave, an upright P wave, an upright T wave, and possibly a small Q wave. When the heart was vertical and the axis was shifted to the right, the normal pattern Lead aV_L was similar to that obtained from the normal right precordial Leads V_1 and V_2 , and consisted of a small R wave, a prominent S wave, and variable P and T waves. The basic pattern in Lead aV_F in vertical hearts when the axis was shifted to the right resembled the left precordial Leads V_5 and V_6 , since the left ventricle faced the left leg. When the heart was horizontal and the axis was shifted to the left, the normal pattern in Lead aV_F resembled the right precordial Leads V_1 and V_2 . When the heart was intermediate in position, and the potential changes of the left ventricle were transmitted to both the left arm and the left leg, both aV_F and aV_L resembled the left precordial Leads V_5 and V_6 , but neither had very great voltage. When the QRS complex was upright in both aV_L and aV_F , that lead which most nearly resembled the left ventricular leads more clearly reflected the position of the heart (Fig. 6;

Q wave in aV_L and V_5). The right arm lead, as can be seen from the figures, almost invariably was negative through most of the QRS interval. This is probably due to the fact that the right arm usually faces the cavities of the heart, which are essentially electronegative, since the spread of activation is toward the epicardium, from the endocardium. The QRS complex in Lead aV_R was variable and consisted of either a QS complex, a small R, deep S, and small R', or a deep Q and small R wave. The R or R' in Lead aV_R rarely exceeded 3.0 mm. and in none of our normal subjects exceeded 5.0 millimeters.

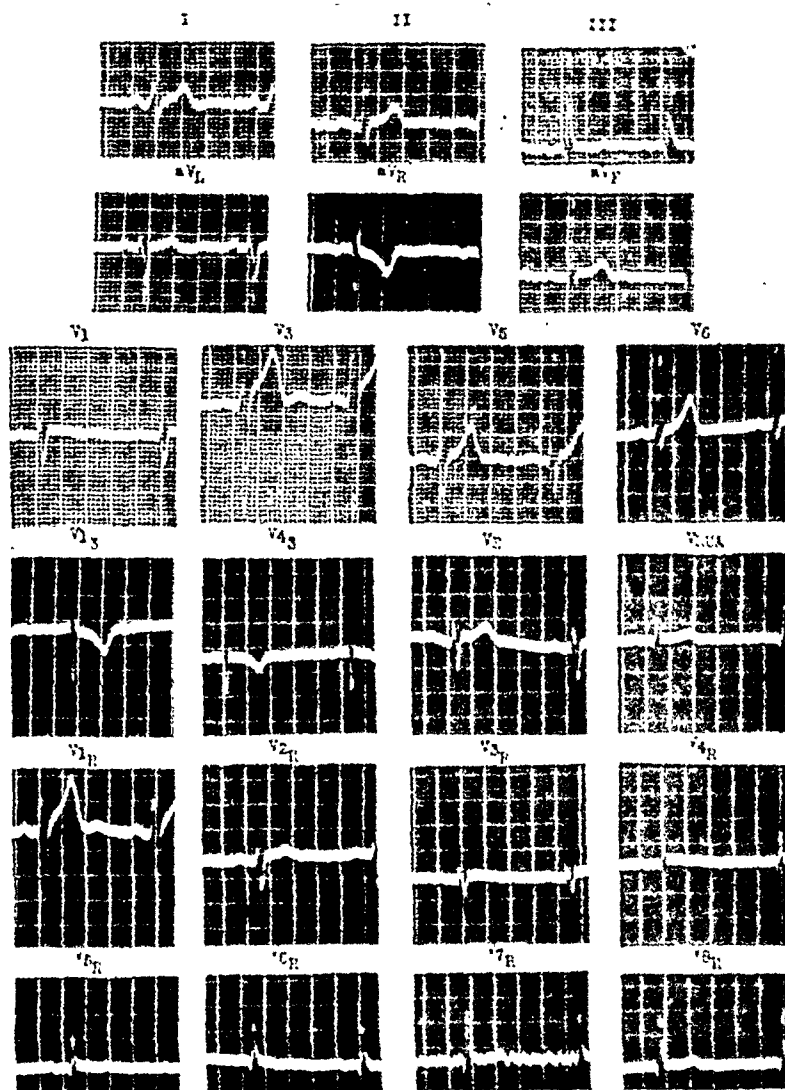


Fig. S.—W. D. L., man, age 20, U150427. March 18, 1948. Left hydrothorax in 1938. Fibro-calcification left upper pulmonary lobe. No cardiac enlargement. Unusual pulsation in left superior cardiac border. Transitional zone between Positions 5 and 6. Left ventricular complexes in V_2 , V_{4S} to V_{5R} (right side), and V_{RUA} (right upper abdomen). Right ventricular complexes in V_1 to V_2 , V_{1L} to V_{2R} , and V_6 . Marked clockwise rotation of heart.

The right arm lead, aV_R , may show a small initial R wave and still reflect the potential changes of the right ventricular cavity, since intracavity leads may reveal a small initial R wave from the right ventricular cavity^{23,24,25} The P wave in Lead aV_R was usually inverted, the RS-T segment isoelectric or slightly depressed, and the T wave always inverted. In none of the normal subjects was an upright T wave found in aV_R .

DISCUSSION

The importance of clearly defining the normal range of the values in the unipolar leads is self-evident, especially when borderline findings require interpretation. The frequency or rarity of a given finding in normal subjects will permit a statement as to the probability of the normality of the finding in question. Furthermore, a knowledge of the approximate percentage in which several given findings may be expected in normal subjects will allow interpretation to be more accurate, since infrequent abnormalities, when multiplied, are geometric and not additive in significance. Thus, in a young patient with hypertension, the presence of the following findings individually would be borderline:

1. A horizontal heart with marked left axis deviation, *or*
2. A relatively low to flat T wave in Leads I, V_5 , or aV_L , in the presence of tall R waves in these leads, *or*
3. A ventricular activation time of 0.55 second in V_6 , *or*
4. A heart with the voltage of R in $V_5 + S$ in $V_1 = 35$ millimeters.

But if several or all of the findings were present together, the chances that these several abnormalities (each to be expected infrequently in normal subjects) were without significance would be remote indeed.

The importance of the unipolar precordial and extremity leads in permitting a more rational interpretation of the electrocardiogram became obvious during the study. Variations in the standard limb leads which previously had been interpreted on an empirical basis were explained more rationally by a consideration of such factors as the electrocardiographic position of the heart, the position of the transitional zone, and the rotation of the apex of the heart either anteriorly or posteriorly on a transverse axis, or in a clockwise manner on a longitudinal axis, et cetera. Proper interpretation of unusual rotation of the normal heart is most important, because records obtained in such cases simulate ventricular hypertrophy or myocardial infarction and the differentiation is obviously of great significance. The standard limb leads are indirect leads and the data obtained from them are not comparable to the data obtained by direct leads from the epicardium in animals or by precordial leads in human subjects. The standard limb leads are bipolar leads and record the composite differences in potential of two unipolar extremity leads and not that of a single extremity. The two unipolar extremity leads used in recording a standard limb lead may each have potential changes which may be additive or may neutralize each other, so that the standard limb lead may not permit the actual condition to be visualized. The standard leads, furthermore, reflect the contri-

bution of all portions of the heart, and the effects of small lesions may be overshadowed by the effect of the great mass of normal myocardium. Multiple precordial leads permit visualization of both right and left ventricular changes, whereas a single precordial lead, if it constitutes the sole evidence presented, has the disadvantage of reflecting potential variations largely of that portion of the heart which lies under the electrode.¹ With variations in the position of the transitional zone and unusual rotation of the heart, a fixed position for a single precordial lead would obviously create many difficulties in interpretation. Furthermore, accurately relocating the exact precordial position when serial records are required, as in myocardial infarction, is most difficult, and multiple leads most easily allow serial changes to be interpreted.

The significance of a small R' deflection in V₁, which was noted in about 5 per cent of the normal subjects (Fig. 4B), is not clear. Exploratory leads over the right precordium failed to give additional information unless they revealed more definite evidence of delayed conduction through the right ventricle. The conus of the right ventricle is the last part of the right ventricle to be activated,¹⁸ and it is possible that this late R' deflection represents activation of this area or of the posterior surface of the left ventricle.²¹ The R' in our cases usually was small, less than 0.04 second in duration, and the initial small R and prominent S deflections were similar to the typical ventricular complex obtained over the normal right ventricle. Serial records in these cases occasionally revealed a small, late R' deflection on one occasion and a notched S without an R' deflection in another. When the R' was taller than the initial R wave and was 0.04 second or more in duration, when the S wave was small and the total QRS complex was 0.10 second or more, the possibility of an incomplete or complete right bundle branch block was considered.

The rarity of a horizontal position of the heart in individuals under the age of 40 years was a surprising finding. This was particularly true in many robust, slightly obese, and sthenic individuals. Only two of our subjects under the age of 39 years had a semihorizontal or horizontal heart. The finding, therefore, of a horizontal heart in a young individual should raise doubts of normality, particularly if an anatomic cause of such a cardiac position is not obvious.

The data on voltage and on the various ratios presented were of value in a companion study on right and left ventricular hypertrophy.⁹⁻¹⁰ Abnormal voltage of the QRS complex often was the initial finding in left ventricular hypertrophy, and the data on voltage presented in the present series of 150 normal subjects have not required change in a review of 1,500 subsequent normal unipolar records taken in the Electrocardiographic Department of the University of California Hospital.

Quantitative data presented on the height of the normal T wave may prove helpful in determining the normality of the troublesome low T wave. Since depolarization has a definite relationship to the succeeding repolarization, the height of the T wave was related to the height of the R wave in the same lead. Our data indicate that a T wave less than 10 per cent of the height of the R wave in the left precordial leads is to be viewed with suspicion (Table VII).

The wide range of the normal variations of the Q wave in the left arm Lead aV_L requires conservatism in the interpretation of the significance of such a finding. The sole use of a percentage figure in relation to the R wave is unreliable because of the occasional high Q/R ratios in normal subjects with small QRS complexes in Lead aV_L , and because of unusual rotation of the heart so as to direct the potentials of the ventricular cavities toward the left arm. The interpretation is at times made more difficult because in different complexes in the same lead, or in different leads on the same or on succeeding records, the QRS complex in Lead aV_L may at one time consist of a QR pattern, and at other times of an rSr' or rS type of complex. This variability may be seen also in high left precordial exploratory leads, when in successive positions the QRS complex may consist of an rSr' or of a QR pattern (Fig. 3). Inspection of these records suggests that these normal Q waves are sharp and of short duration, and not associated with characteristic RST-T changes of coronary insufficiency. Whether the QR complex in Lead aV_L is due to posterior rotation of the heart on a transverse axis, as suggested by Goldberger,⁷ cannot be proved from our data.

SUMMARY AND CONCLUSIONS

1. A statistical study of the unipolar precordial and extremity leads of 150 normal subjects is presented.
2. The mean, standard deviation, and the range of the amplitude of the Q, R, S, and T waves and of the ventricular activation time (time of onset of the intrinsic deflection) have been determined in these normal subjects and tabulated.
3. To present certain of the data in further detail, the following ratios and sums have been determined and their significance discussed: (a) the Q/R ratio; (b) the R/T ratio; (c) the R/S ratio; (d) the R/S ratio in V_5 divided by the R/S ratio in V_1 ; (e) the sum of the amplitudes of the R wave in V_1 and the S wave in V_5 ; (f) the sum of the amplitudes of the S wave in V_1 and the R wave in V_5 .
4. The electrocardiographic position of the heart in these normal subjects is discussed, and the infrequency of a horizontal heart in persons under the age of 39 years (in the absence of gross obesity or late pregnancy) is pointed out.
5. The variability of the Q wave in the left arm lead is described, and the significance of total QRS amplitude, rotation of the heart, and other factors important to proper interpretation are discussed.

We are grateful to Miss Julia Haug, Miss Nancy Gelardi, Mrs. Doris Tuttle, and Mrs. Angelina Galante for technical assistance, and to Dr. John C. Talbot for advice in regard to the statistical methods.

REFERENCES

1. Wilson, F. N., and others: The Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
2. Sodi-Pallares, D.: *Neuvas bases de Electrocardiografia*, Edic. del Inst. Nat. de México, 1945.

3. Goldberger, E.: An Interpretation of Axis Deviation and Ventricular Hypertrophy, *AM. HEART J.* 28:621, 1944.
4. Sokolow, M.: Present Concepts of the Clinical Significance of Unipolar Precordial Electrocardiograms, *California Med.* 65:151, 1946.
5. Myers, G. B., and Oren, B. G.: The Use of the Augmented Unipolar Left Leg Lead in the Differentiation of Normal From Abnormal Q Wave in Standard Lead III, *AM. HEART J.* 29:708, 1945.
6. Goldberger, E.: The Differentiation of Normal From Abnormal Q Waves, *AM. HEART J.* 30:341, 1945.
7. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger.
8. Myers, G. B., Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, *AM. HEART J.* 35:1, 1948.
9. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, *AM. HEART J.* 37:161, 1949.
10. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, *AM. HEART J.* In press.
11. Salazar, M. M., and Sodi-Pallares, D.: Estudio Sobre el Corazon Pulmonar Cronico: Analisis de 14 Casos, *Arch. Inst. cardiol. México* 16:22, 1946.
12. Kossmann, C. E., and Johnston, F. D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and the Extremities in Normal Subjects, *AM. HEART J.* 10:925, 1935.
13. Battro, A., and Mendy, J. C.: Precordial Leads in Children, *Arch. Int. Med.* 78:31, 1946.
14. Sodi-Pallares, D., Para, O., Cabrera, E., and Mendoza, F.: La Deflexion Intrinseca en Casos Normales y en Hipertrofias Ventriculares, *Arch. Inst. cardiol. México* 16:397, 1946.
15. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, *AM. HEART J.* 31:785, 1947.
16. Vaquero, M., Lason, R. L., and Lason, A. L.: Electrocardiograma Normal Estudio de 500 Casos en Derivaciones Standard y Unipolares, *Arch. Inst. cardiol. México* 17:155, 1947.
17. Goldberger, E.: A Simple, Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar Extremity Leads, *AM. HEART J.* 23:483, 1942.
18. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II. The Ventricles, *Phil. Trans. Roy. Soc. London, Series B* 206:181, 1915.
19. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* 30:162, 1919.
20. Hecht, H.: Brustwandableitungen in der klinischen Elektrokardiographie, *Deutsches Arch. f. klin. Med.* 179:1, 1936.
21. Rosenbaum, F. F., Wilson, F. N., and Johnston, F. D.: The Precordial Electrocardiogram in High Lateral Myocardial Infarction, *AM. HEART J.* 32:135, 1946.
22. Bierman, H. R., Rapoport, E., Sokolow, M., and Edgar, A. L.: Unpublished data.
23. Hecht, H. H.: Potential Variations of the Right Auricular and Ventricular Cavities in Man, *AM. HEART J.* 32:39, 1946.
24. Sodi-Pallares, D., Vizcaino, M., Soberon, J., and Cabrera, E.: Comparative Study of the Intracavity Potential in Man and in Dog, *AM. HEART J.* 33:819, 1947.
25. Kossmann, C. E., Berger, A. R., Brumlik, J., and Briller, S. A.: An Analysis of Causes of Right Axis Deviation Based Partly on Endocardial Potentials of the Hypertrophied Right Ventricle, *AM. HEART J.* 35:309, 1948.

THE HEART MUSCLE AND THE ELECTROCARDIOGRAM IN CORONARY DISEASE

II. DIFFICULTIES OF DESCRIPTION AND ILLUSTRATION OF VENTRICULAR MUSCLE LESIONS, WITH A METHOD FOR THEIR GRAPHIC REPRESENTATION IN A MYOCARDIAL MAP

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WITH the progress which has been made in clinical and electrocardiographic diagnosis of myocardial damage, the precise localization of lesions at autopsy has become essential. In the first paper of this series the principles of a pathologic technique adequate for clinicopathologic correlation studies have been considered.¹ This second paper is concerned with the organization of the pathologic data once they have been collected. Systematic gross and microscopic scrutiny of the myocardium is only the first step in the study of infarcts and scars. The information gained cannot be put to use until it has been adequately recorded in some permanent form. This is not easy. The heart muscle and its lesions are difficult to describe in words or to illustrate in pictures. Indeed, all writing about the myocardium has suffered from the inadequacy of descriptive and illustrative methods.

The present study discusses the difficulties of describing myocardial damage verbally, the necessity for resort to pictorial methods of recording, and the reasons why such methods of illustration have been unsatisfactory. A solution to the problem is offered on the basis of a geometric survey of the damaged areas seen in serial slices, which permits graphic representation of lesions and their important anatomic relationships. A convenient schema or myocardial map of the left ventricular and septal muscle and the major coronary branches will then be described for use in the presentation of data in subsequent sections of the report.

THE DEFECTS OF VERBAL RECORDS

The standard terminology for cardiac ventricular areas is in itself a major difficulty. The usual divisions are right and left ventricles, apical and basal regions, and various surface areas: anterior, lateral, posterior, and perhaps diaphragmatic, for each chamber. Endocardial areas have been named from

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This investigation was aided by a grant from the Life Insurance Medical Research Fund, beginning July 1, 1947.

the overlying surface, except for the part without any epicardial surface, the septum. While these terms sound simple and definite, they are seldom defined, and are used as if they referred to clear-cut subdivisions of the heart, with the same meaning for clinician and pathologist.

It is usually forgotten that the heart is so lacking in convenient landmarks that even under the most favorable circumstances, for example when the pathologist has the organ in his hands, it is difficult to establish the limits of surface areas except along the interventricular grooves. The anterior, lateral, and posterior regions fade gradually into each other so that their limits are mainly arbitrary. As a rule, the middle of the lateral wall of the left ventricle is taken to lie halfway between the anterior and posterior grooves, the anterolateral and posterolateral regions being somewhere intermediate. The conventional subdivisions of the left ventricular circumference are thus not very precise. They are especially unsatisfactory near the apex or near the endocardial surface, where distances are much shorter. The right ventricular surface is subdivided at the acute margin, which, as a rule, is clearly marked at autopsy.

Intermediate distances between apex and base cannot be measured conveniently at all, since the heart has no transverse landmarks below the atrio-ventricular grooves. Attempts to escape the difficulty by linear measurements are unavailing because the significance of any distance in centimeters will vary with the size of the heart and the position at which the measurement is made. It has generally been found best to make rough subdivisions of the distances between such landmarks as there are, making reference to such areas as "the apical third of the posterolateral wall," "the anterior basal portion of the septum," and so forth. Clearly, however, the pathologist consciously or unconsciously is relating everything (in a not very quantitative way) to the atrio-ventricular and interventricular grooves and the left ventricular apex.

To the clinician, on the other hand, the position of the interventricular grooves and, hence, of the adjacent myocardium cannot be accurately known. Study of the cardiac silhouette or of the precordial patterns of the electrocardiogram provides data about pulsation, contour, and electrical activity which may vary greatly in anatomic significance with the position of the heart in the chest. Furthermore, with the rare exception of conveniently placed calcification, there is no way of estimating with certainty the relation of the post-mortem position of the heart in the chest to that during life.

Despite these difficulties, the same terms are used by both clinician and pathologist. Identical words may thus have considerably different meanings. "Anterior" to the pathologist means proximity to the anterior interventricular groove, regardless of the heart's position in the chest. To the clinician, "anterior" may mean the parts of the heart presented to the precordium or even the myocardium affected by anterior descending coronary artery occlusion. "Posterior" has an analogous variety of meanings and in addition is often not clearly distinguished from "diaphragmatic" and "posterolateral" so far as the left ventricle is concerned. "Lateral," for the clinician, means the part of the left ventricle he sees pulsating fluoroscopically which is directed toward the left axilla and shoulder and separated from the chest wall by lung. The

muscle actually comprising this region will, of course, vary, in the pathologist's terms, from "anterolateral" to "posterolateral," depending on cardiac rotation. "Subendocardial" is vaguely used by both the clinician and the pathologist. In general, it means the myocardium that lies nearest the ventricular cavities, designating a lack of surface involvement, but it is seldom stated whether the term refers to the trabeculae carneae, the underlying wall proper, or both.

As a result of the loose employment of a nomenclature that was never very exact, it is only possible to specify myocardial areas precisely by tacking on qualifying and explicatory terms. Autopsy reports thus become more wordy and involved as their accuracy increases; yet protocols which sound simple and clear are very likely to be inadequate.

While the gross anatomic form of the ventricular muscle mass, in the substance of which lesions lie, is difficult to describe as a whole or to divide into smaller regions, this is only part of the descriptive difficulty. Infarcts and scars conform in shape not to the conventional subdivision of the ventricles but to the areas of distribution of the epicardial coronary arteries. Yet these areas show enough anatomic variation from anomaly or collateral circulation to be unsuitable as a basis for indicating the shape of lesions. Moreover, the infarcts and scars themselves, far from resembling the simple circular, oval, or wedge-shaped areas conventionally described in medical literature, appear as curved, plate-like areas of fibrosis or necrosis which have irregular borders and may vary in thickness in different parts of the ventricular wall. Although generally discrete and clear-cut in their form, these lesions are so poorly adapted to verbal description that no reforms in nomenclature seem to offer hope in solution of the difficulty.

On the other hand, forms difficult to describe are often easy to draw. A number of investigators, noting this, have supplemented their protocols by pictures. Though the heart also resists illustration stubbornly, there seems little question but that this is a more fruitful approach. Prior to 1935 not many investigators were interested in myocardial illustration, but since that time there have been more systematic attempts to supplement protocols by photographs, drawings, or both. It is worth while to examine some of these methods.

METHODS OF ILLUSTRATION

Of the few investigators who have used photographs for the routine recording of lesions, one group deserving special mention is Büchner, Weber, and Haager (1935),² whose monograph illustrated myocardial damage by combining photography with an unusual method of opening the heart. A longitudinal slice was made down the lateral wall of the left ventricle and carried through the center of the septum to the anterior right ventricular wall, almost cutting the heart into anterior and posterior halves. The limits of any lesion that photographed poorly were indicated by a line drawn on the photographic print (Fig. 1). This had to be done frequently, since the greater part of most lesions was buried in opaque muscle.

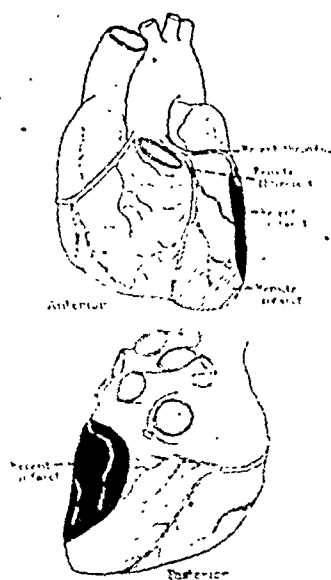
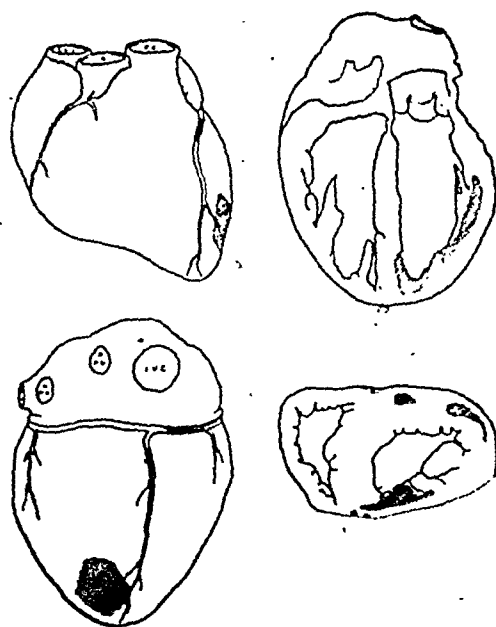
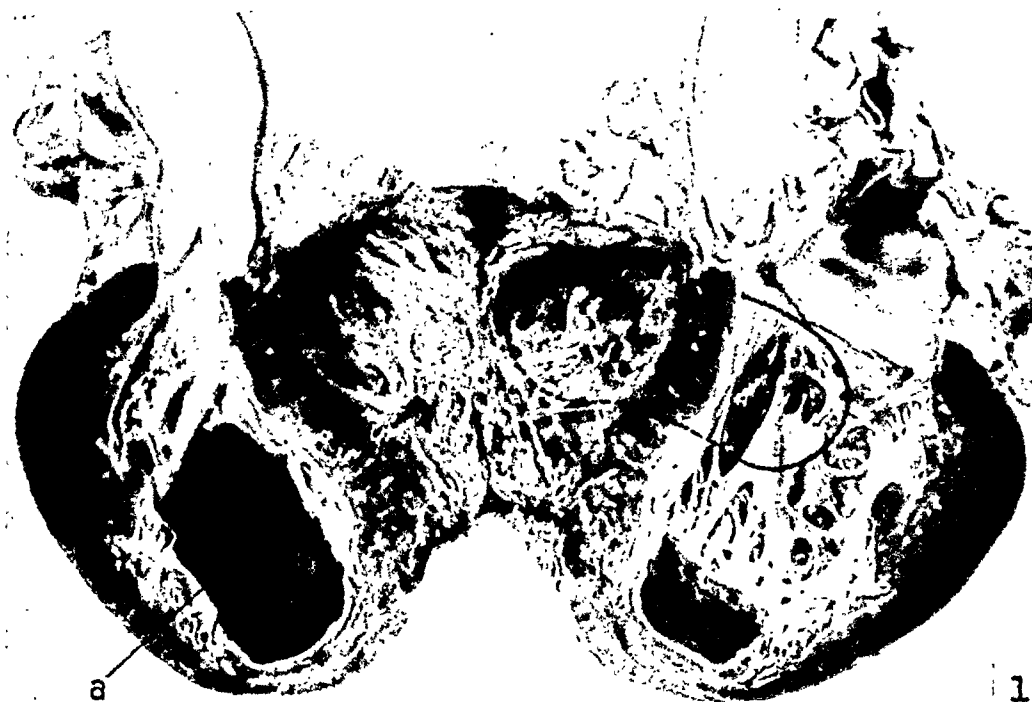


Fig. 1. —A heart cut into anterior (left side of photograph) and posterior halves. An old, large "anterior" lesion involves the apex and septum. (a). A recent "posterior" lesion that does not show well in the photograph has been indicated by the heavy line (solid in the left ventricle, broken in the right). (From Büchler and associates, 1935.²)

Fig. 2.—Areas of scarring in diagrams of the external surfaces (left), a single longitudinal slice (upper right), and a single transverse slice (lower right). (From Burton and associates, 1930.³)

Fig. 3.—An old "anterior" and a recent "lateral" lesion, with the related coronary lesions, are indicated on conventional anatomical drawings of the exterior of the heart. (From Thomson and Fell, 1944.⁴)

Photography has not proved a good method for recording routinely the appearance of infarcts and scars. An occasional lesion may be displayed well, but many scars show up poorly in photographs; the color changes in acute lesions, which are often subtle, fail to be recorded, while irregularity of fixation, obvious to the eye, may be deceptive in a picture. Furthermore, the consistency of tissue, almost as important as color in the gross evaluation of lesions, cannot be recorded by the camera. At best, photographs provide an incomplete report and almost always require supplementation or retouching.

Several types of drawings have been employed in the last two decades to illustrate myocardial lesions. Burton and associates (1930),³ in their four case reports, drew the outline of scars on a diagram of the uncut heart, supplementing this by sketches of a single longitudinal and transverse slice of the ventricles (Fig. 2). Thomson and Feil (1944)⁴ used a similar type of drawing of the cardiac surfaces (Fig. 3). Jervell (1935)⁵ indicated the site of lesions in a sketch of the routinely opened left ventricle as seen on its endocardial aspect, the lateral wall flap being turned back and the septal wall exposed (Fig. 4). Saphir and associates (1935)⁶ adopted the Spalteholz schema of the coronary circulation⁷ (Fig. 6) to a sketch of the partly opened heart (Fig. 5). Schlesinger (1938),⁸ in his studies of the coronary circulation, further modified the Spalteholz schema by actually dissecting the heart so that its main epicardial arteries could be laid in one plane for radiographic study. The method consists essentially of cutting out the septum. This converts the heart into a muscular bag which, after being opened longitudinally down the anterior interventricular groove, can be laid flat. The technique is, of course, designed primarily to produce a picture of the coronary arteries, but has been also used to indicate the position of areas of myocardial damage by outlining them on the roentgenogram⁸ (Fig. 7) or on a drawing made therefrom.⁹ This method has acquired considerable popularity.

There are serious disadvantages to all the illustrative methods mentioned so far. In the first place, none of them shows the heart in a manner well fitted for the display of its most common muscle lesions. Much space is given to the right ventricle, where large lesions are rare. This is accomplished at the expense of proper illustration of the septum, which has to be made a subsidiary part of the picture or shown as a separate fragment. Since the septum is often infarcted, the infrequent reporting of its lesions testifies to a frequent failure in exploration or illustration of this region. Furthermore, with the exception of Büchner's illustrations,² no investigators have provided in their drawings a record of the thickness of the heart wall affected by myocardial lesions. The types of illustration chosen have thus tended to affect unfavorably the data collected. It is unfortunate that certain types of myocardial lesions which are difficult to record have proved to be common and important.

Second, none of the illustrative methods shows lesions in such a way that they can be related to familiar cardiac landmarks. It happens that while the greater part of myocardial damage is found in the deeper layers,¹⁰ the interventricular grooves which define the limits of the right, left, and septal ventricular musculature are on the outer surface of the heart. When the inside of

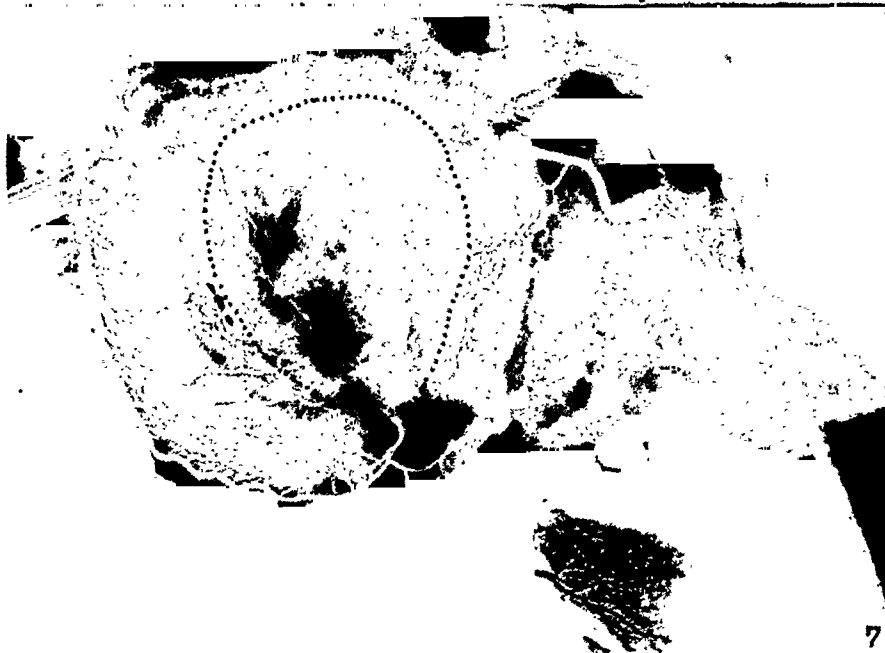
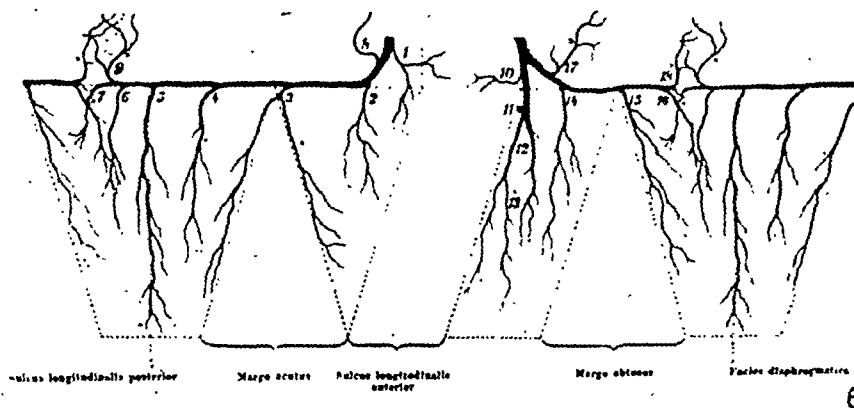
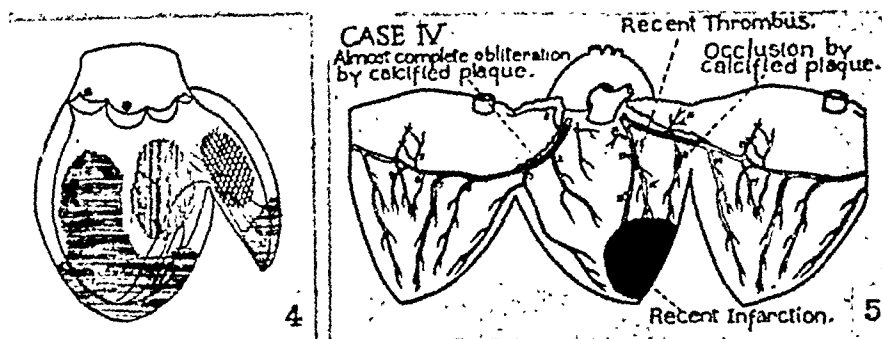


Fig. 4.—A large "anterior" lesion and small "lateral" and "posterior" lesions have been indicated on a drawing of the opened left ventricle. (From Jervell, 1935.⁵)

Fig. 5.—A recent "anterior" lesion and related coronary lesions are indicated on a diagrammatic compromise between the routine Virchow method of opening the heart and the Spalteholz schema (see Fig. 6). (From Saphir and associates, 1935.⁶)

Fig. 6.—A diagrammatic representation of the main surface coronary arteries as they appear when laid flat. No septal branches are shown. (From Spalteholz, 1924.⁷)

Fig. 7.—A roentgenograph of a heart in which a large "posterolateral" lesion has been indicated by the dotted line. The heart has been opened by a special technique which enables the main arteries to be flattened out in one plane. The septum has been cut out and appears as a separate piece. (From Schlesinger, 1938.⁸)

the heart is illustrated (Jervell⁵ and Büchner and associates²), the lesions are shown best but the landmarks are not evident; when the outside is illustrated (Thomson and Feil⁴ and Saphir and associates⁶), the landmarks are seen well but the lesions are not. In either circumstance the general reader tends to lose his bearings when looking at the illustration, which thus fails of a good deal of its purpose in making the relevant pathologic anatomy clear, especially where electrocardiographic correlation is a main objective.

The third disadvantage arises from the second. Because the relation of damaged myocardial areas to standard landmarks is not established, transfer of data from the anatomical specimen to any of the illustrations so far discussed can only be done in an approximate way, unless the heart has been opened exactly in the manner depicted by the particular illustration. An accurate sketch or a retouched photograph can then reproduce the appearance of the specimen, but the price is likely to be a less satisfactory autopsy. The best form of illustration for the heart is not ordinarily a picture of the fragments which result from a dissection thorough enough to obtain complete facts. Systematic exploration of the heart muscle thus has tended to be discouraged rather than stimulated by the employment of the usual illustrative techniques.

There is, nonetheless, a real need for depicting lesions in the heart muscle. The disadvantages of the usual methods—their poor adaptation to the common types and characteristics of muscle damage, their failure to relate lesions to standard landmarks, and their tendency to interfere with the thoroughness of an autopsy—call for improvement in, but not abandonment of myocardial illustration. Indeed, the very analysis of the disadvantages makes it possible to formulate the principles which must underlie any adequate pictorial description of this sort.

The first consideration must be a *pictorial record* which preserves the findings of a thorough autopsy in permanent, accurate, and complete form. Because of the deficiencies of verbal description, already discussed, the pictorial record must replace the cumbersome and less precise written protocol. Second, it will usually be necessary for the purposes of any particular investigation to select from the full pictorial record those facts which bear directly on the problem at hand and make another illustration more suited to easy analysis of data and comparison of hearts throughout a series of cases. This second type of illustration may be called a *selective or reconstructive schema*, its primary purpose being not to record data but to display them in a useful way. Both types of illustration are valuable, but it is clear that the second type is dependent on the first. The pictorial record must be adequate; otherwise no worthwhile selective schema can be based on it. Most illustrations of the heart fail both as accurate records and as convenient schemata because they attempt too much in a single picture. The solution of the problem is to keep the two steps—recording and reconstructing—quite separate, proceeding to the second step only after the first has been accomplished.

THE SERIAL SLICE TECHNIQUE AS A BASIS FOR RECORDING DATA

There is little question as to the optimal method of making a pictorial record of the myocardium. Since serial slicing is the most accurate and thorough method available for the exploration of the muscle,¹ a set of drawings or retouched photographs of the slices themselves provides a logical and satisfactory record of the gross findings (Fig. 8). The sites of microscopic sections can be readily shown. Color photographs of any or all slices can be taken when practical. It is easy, moreover, to preserve representative slices for future reference.

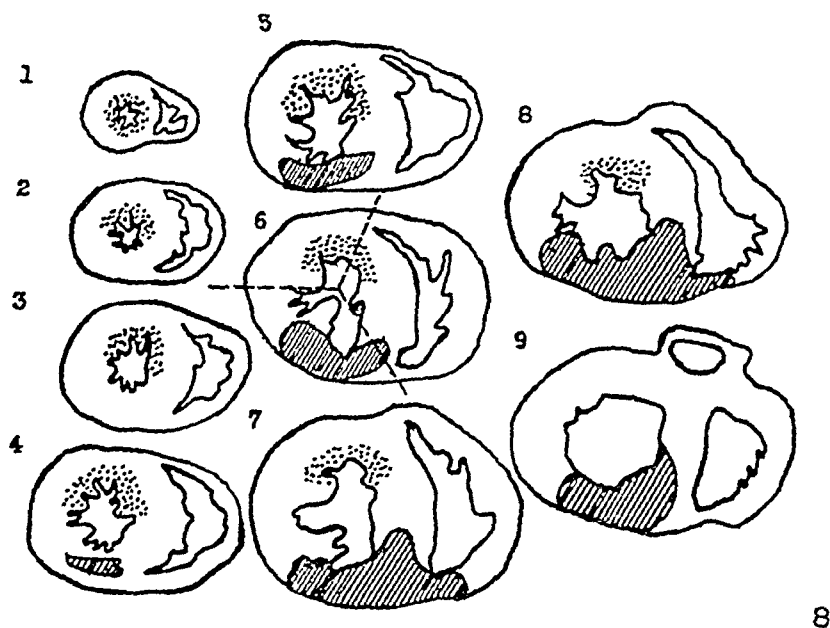


Fig. 8.—Drawing made of the slices from a heart which contains a large, recent "posterior" infarct (shaded) and an old "anterior" scar (stippled). The slices have been numbered beginning at the apex. The anterior surface of each slice is toward the top of the page and the observer views the basal aspect of each slice.

It is rather surprising that illustrations of serially sliced hearts have not been used more frequently. To our knowledge, only Lowe¹² and Kossmann and De La Chapelle¹¹ have used this method systematically for correlation purposes prior to our adoption of it in 1940. Since then, Myers and associates¹³ have adopted serial slicing, making drawings of the gross shape of muscle lesions on roentgenograms of injected slices. With these exceptions and the case reports by Burton and associates⁵ and Price and Janes,¹¹ serial slice illustrations have been used only in sporadic fashion to demonstrate particular points of cardiac anatomy. Their employment in this capacity goes back many years, good cross-sectional drawings of the heart being available in Tandler's

monograph (1913).¹⁵ More recently Gross and Kugel (1933)¹⁶ have used serial slicing to demonstrate roentgenographically the intramyocardial distribution of injected coronary arteries. The realization that the systematic use of serial slice drawings forms a superior autopsy record seems to be of recent origin.

Pictorial records based on serial slices have many advantages in addition to their completeness and precision. The ventricular anatomy is simpler and clearer in cross section than in any other way of opening the heart. The left ventricle and the septum are seen as a heavy circular ring of muscle, about equally thick everywhere save for the papillary muscles. The right ventricle appears as a thin-walled angular or crescentic structure attached to one side of the main muscle mass.

Infarcts and scars are found almost exclusively in the left ventricular-septal muscle ring, especially its inner aspect. The right ventricular walls are seldom infarcted massively and almost never alone, small extensions from predominantly left ventricular lesions being the usual finding. For purposes of coronary disease study, therefore, the main attention can be given to the left ventricle and septum, which form a structure far simpler to deal with than an entire heart. It should be noted that all the standard cardiac landmarks are seen as clearly in serial sections as in the intact or routinely opened heart.

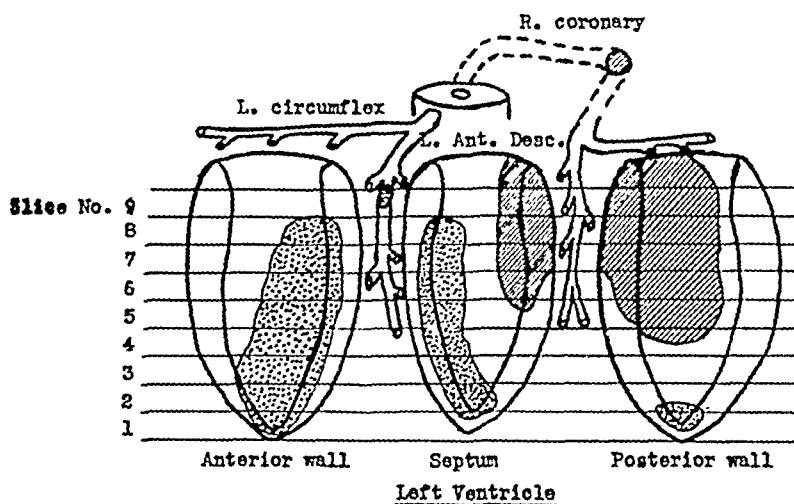
The simplicity of their cross-sectional form makes measurement of the left ventricular and septal myocardium comparatively easy. Axial measurements, from apex to base, are provided by the slices themselves, if they have been cut in uniform fashion. For circumferential measurements, the interventricular grooves provide fixed points, clearly visible in each slice, on the left ventricular-septal muscle ring. It is convenient and logical to draw three radii on the sketches of the slices, from the center of the left ventricular cavity through each groove and the middle of the lateral wall, thus dividing the ventricle into anterolateral, posterolateral, and septal segments (Fig. 8, Slice 6). These correspond to the conventional anatomic areas of the heart and can be further subdivided as the investigator sees fit. For radial measurements, from the left ventricular cavity outward, the thick segments of the left ventricle and septal wall can be arbitrarily divided into halves, thirds, or quarters.* It will then be possible to state where any damaged area in the left ventricular and septal myocardium is in terms of axial, circumferential, and radial units. In a word, a coordinate system is set up for that muscle area where the great bulk of myocardial damage occurs. The substance of the right ventricle can be subdivided, though in a somewhat less satisfactory fashion, by use of the margo acutus as the circumferential reference point for separating the anterior and diaphragmatic regions.

In this manner damage can be recorded accurately, the anatomic relationships of the ventricular muscle mass can be clearly envisaged, and the position of any point in the heart can be stated precisely in terms of axial, circumferen-

*It is not usually practical to differentiate the layers of the wall on the basis of muscle bundles (though this could be done), because the number and arrangement of anatomic muscle layers varies in different parts of the ventricles.

tial, and radial coordinates. The only disadvantage of any autopsy report in this form is that ten or twelve pictures have to be looked at for every heart studied. The lesions, divided into parts by the slicing, have to be put together by the imagination. While such a synthesis can be made mentally for any single heart by an experienced observer, a considerable imaginative effort is required, the picture conjured up is fleeting, and it is almost impossible to make comparisons within a series of hearts.

It is therefore convenient to reconstruct the appearance of the heart as it was before it had been sliced (a simple procedure for any organ that has been serially sliced), making the muscle transparent and the myocardial lesions



9

Fig. 9.—A myocardial map of the ventricular lesions shown in Fig. 8, with coronary lesions also shown. The three segments, anterior wall, septum, and posterior wall, are depicted as if cut apart at the interventricular grooves and in the midline of the lateral wall (see Fig. 8, Slice 6). The segments are viewed from their inner aspect, the cut edges displaying the thickness of wall affected by the lesions.

The dotted portion of the right coronary artery represents its course around the base of the right ventricle (not illustrated). The recent infarct (shaded), involving the full thickness of the posterior wall and the adjacent septum, is consequent on recent thrombosis (shaded) of the right coronary artery. The old scar (stippled), affecting the subendocardial region of the apex, the anterior wall, and the left ventricular side of the septum, is related to an organized thrombus (stippled) in the left anterior descending coronary artery.

opaque. Provided such a drawing keeps clear the relation of the lesions to the coordinate system just described, an accurate transfer of data from serial slices to this or any sort of illustration is possible.

A NEW SCHEMA OF THE VENTRICLES OR MYOCARDIAL MAP

We found it best to illustrate the left ventricular-septal muscle mass as it would appear from its endocardial aspect after it had been cut open by radial incisions down the anterior interventricular groove, the posterior interventricular groove, and a line midway between them along the lateral wall, the right ventricular walls having first been cut away. Three triangular pieces of

muscle result from such a procedure: (1) an anterolateral segment bearing the anterior papillary muscle, (2) a septal segment, and (3) a posterolateral segment bearing the posterior papillary muscle.*

The myocardial map (Fig. 9) is a drawing of the appearance of these triangular segments seen from the left ventricular cavity side and placed so that their axes are parallel and their bases at the same level. A series of transverse parallel lines will then correspond to the position of the slices which actually would be used in exploring the myocardium. These constitute lines of latitude for the map. The meridians, or lines of longitude, are the anterior and posterior interventricular grooves, and the midline of the lateral wall of the ventricle. Because the walls of the left ventricle have considerable thickness, it cannot be rolled out flat and is not truly "developable" in the cartographic sense. The map consists of an isometric projection drawing of the segments rather than a flat chart. Since the left ventricular endocardial surfaces of the segments are smaller, their cut edges appear in perspective and are used to indicate the part of the wall involved. This is an important part of the record for left ventricular and septal damage.

The main epicardial rami of the coronary arteries follow the atrioventricular and interventricular grooves. As these positions are also the sites of separation of the segments in our map, these vessels may readily be added to it in schematic fashion. The proximal portion of the right coronary artery is represented diagrammatically to show how its terminal portion reaches the back of the left ventricle by passing around the tricuspid valve ring.

Data accumulated by the slicing technique and recorded by sketches of the slices can be transferred to the myocardial map with as great precision as the investigation seems to demand. On such sketches radial lines drawn from the center of the left ventricle through the anterior and posterior interventricular grooves and the center of the lateral wall divide the main portion of each slice into three segments. These, if piled on top of each other, would correspond directly to the segments of the map. The data from each slice of the myocardium are transferred to the appropriate position of each segment in the map until a reconstructed picture of the lesion is gradually built up.

It is necessary to make a slightly different muscle map for each heart if the anatomical variations in the coronary tree or localized thinning of the heart wall are to be recorded. Mural thrombi and coronary lesions are indicated in the same diagram. The precise position of microscopic sections can be shown. In hearts with multiple lesions, the age of each, as finally determined by microscopic study, is shown by appropriate color or crosshatching. Thus, the whole

*To make a demonstration specimen the dissection proceeds as follows: The auricles having been removed, the free walls of the right ventricle are clipped away close to their attachments at the interventricular grooves and the infundibular area. The remainder of the specimen, a conical chamber with a patch of right ventricle endocardium on its septal side, is opened first along the "lateral" wall, opposite the middle of the septum, and can be partially flattened out after its valve rings have been cut at their juncture. Cuts from apex to base following the course of the interventricular grooves then result in the three segments depicted in the map. The right ventricular specimens can be flattened out by cutting a few trabeculae carneae, and divided along the acute margin to form other map segments if desired.

of the relevant pathologic data may be concentrated in a single diagram, with the interrelationships between coronary and myocardial lesions and the main ventricular landmarks accurately preserved.

DISCUSSION

There is no need to construct a myocardial map in just the form we have chosen. Once lesions have been related to the system of coordinates by drawings made of the slices, a basis is established whereby any type of reconstruction desired may be effected by a purely geometrical rearrangement. The map to be used in this study, however, emphasizes the facts which have proved most fruitful in interpreting and localizing myocardial damage resulting from coronary disease, juxtaposing them so that the eye can grasp readily their most significant interrelationships. The picture of damage seen in the myocardial map is, of course, no more accurate than the record of serial slices actually used for exploring the ventricular muscle. Unlike other schematic illustrations, however, it is no less accurate than the autopsy which it epitomizes.

In the myocardial map the left ventricle is treated as if it were a conical chamber, ringlike in cross section. Its intracardiac portion, defined by radial cuts along the interventricular grooves, is the interventricular septum. Despite the fact that many workers seem to consider this as a sort of international zone, assigned to neither ventricle, there are good reasons for considering it a part of the left.

Functionally, the left ventricle might be considered as composed of all the muscle that directly aids in expelling blood through the aortic ring. Certainly most of the septum appears to take part in this action. Anatomically, the ventricular muscle bundles, in so far as they make any distinction between the chambers, have an arrangement not inconsistent with the concept of septal continuity with the left ventricular walls.* The thickness and curvature of the septum as seen in transverse section (Fig. 8) in no way suggests a passive partition between the ventricular cavities. It is further noteworthy that in hypertension and valvular disease the septum and the left ventricular walls hypertrophy together.

Aside from these reasons, regardless of their cogency, the septum must be treated as part of the left ventricle from the pathologic point of view. Infarcts and scars in the left ventricular walls run into the septum with great frequency, instead of crossing to the right ventricle. The anterior and posterior descending coronary vessels supply it not only by their high septal branches but by multiple penetrating rami throughout their length, and septal anastomoses between right and left coronaries are probably the richest in the heart.^{18,19} The distribution of the coronary circulation would seem hard to understand without attention to the septal vascular bed. Moreover, the lo-

*Of the six main ventricular muscle bands, only one, the scroll (*M. Ventriculorum Circumambiens*), passes into the septum from the right ventricle. The superficial and deep sinospiral and bulbospiral muscles, in so far as they form the septum, enter it from the left ventricle and pass out of it to ramify in the left ventricle again. The longitudinal interventricular muscle starts at the base of the septum, and, having traversed its length, passes also to the left ventricle.¹⁷

cation of the bundle of His in the upper septum makes this a strategic area, in which the localization of myocardial damage might be expected to be of signal importance.

Clearly the septum, or intracardiac portion of the left ventricle, as one might choose to call it,* must form an important part of any diagram of the muscle and not merely an afterthought or a detached fragment; otherwise many important relationships will be destroyed. They are preserved in the type of myocardial map used in this study.

Only the major epicardial coronary branches are illustrated in the diagram. This ordinarily suffices, as it is generally agreed that coronary sclerosis is limited mainly to these larger, dissectable channels. It is our experience that myocardial damage almost always shows a close correlation with the distribution of stenosis and occlusions in the proximal portions of these larger vessels. In any unusual case, however, it is easy to adjust or amplify the map.

SUMMARY AND CONCLUSIONS

The complex data resulting from thorough exploration of the heart muscle in coronary disease present problems of recording and illustration which must be solved before a clinicopathologic correlation study of any series of patients can be accomplished. The character of the ventricular anatomy, the shape of infarcts and scars, and the defects of the standard nomenclature make verbal description of autopsy findings unsatisfactory.

The usual methods of illustration fail both as complete pictorial records of myocardial damage and as useful epitomes of the relevant pathologic facts and their important interrelationships. When hearts have been studied by a method which divides the ventricles into transverse slices, accurate drawings of the slices make excellent records.

From an adequate pictorial record, it is possible to construct a graphic representation, or myocardial map, of arterial and muscle lesions. A convenient map of the left ventricular and septal muscle is described, which permits concentration of all relevant pathologic data in a single diagram.

Combination of the serial slice method for examining and recording with the myocardial map for reconstructing, correlating, and illustrating data provides an efficient deployment of standard techniques for the localization and interpretation of muscle damage. If the possibilities of these and similar methods are more fully explored, clinical and electrocardiographic diagnoses can be placed on a much more solid footing, and the clearer understanding of the natural history of coronary disease thus gained should permit better evaluation of the results of therapy.

*Richard Lower (1631-1690)²⁰ had observed: "The wall of the right ventricle is much thinner and is attached to the side of the left ventricle like some appendage; . . . describing only half a circle in its movement. . . . The septum helps the contraction of the left ventricle only . . . and, indeed, it could not be otherwise since this septum is part of the left ventricle, and its fibers are continuous everywhere with the general surface of the left ventricle and merge into it."

REFERENCES

1. Sheldon, W. F., and Sayen, J. J.: The Heart Muscle and the Electrocardiogram in Coronary Disease. I. Survey of Standards and Methods for Obtaining the Anatomic Data Requisite for Clinicopathologic Correlation, *Am. Heart J.*, 38:517, 1949.
2. Büchner, F., Weber, A., and Haager, B.: *Koronarinfarkt und Koronarinsuffizienz*, Leipzig, 1935, Georg Thieme.
3. Burton, J. A. G., Cowan, J., Kay, J. H., Marshall, A. J., Rennie, J. K., Ramage, J. H., and Teacher, J. H.: Four Cases of Fibrosis of the Myocardium With Electrocardiographic and Post-mortem Examinations, *Quart. J. Med.* 23:293, 1930.
4. Thomson, H. W., and Feil, H.: Infarction of the Lateral Wall of the Left Ventricle: Pathologic and Electrocardiographic Study, *Am. J. M. Sc.* 207:588, 1944.
5. Jervell, A.: *Befunde bei Herzinfarkt*, *Acta med. Scandinav. Suppl. L. A. . . .*
6. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, *AM. HEART J.* 10:567, 1935.
7. Spalteholz, W.: *Die Arterien der Herz wand*, Leipzig, 1924, S. Hirzel.
8. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15:528, 1938.
9. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathological Findings, *AM. HEART J.* 19:1, 1940.
10. Wolferth, C. C., Sayen, J. J., and Sheldon, W. F.: The Anatomy of Acute Infarcts and Scars in the Heart With Reference to Electrocardiographic Diagnosis, *Tr. A. Am. Physicians* 60:138, 1947.
11. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction.
 - I. Observations on Cases With Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, *AM. HEART J.* 15:70, 1938.
 - II. Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, *AM. HEART J.* 18:344, 1939.
 - III. Observations on Cases in Which the Lesions Were Diffuse, *AM. HEART J.* 18:352, 1939.
12. Lowe, T. E.: The Significance of Myocardial Scars in the Human Heart, *J. Path. & Bact.* 49:195, 1939.
13. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, *AM. HEART J.* 34:785, 1947.
14. Price, R. K., and Janes, L. R.: A Case of Subendocardial Myocardial Infarction, *Brit. Heart J.* 5:134, 1943.
15. Tandler, J.: *Anatomie des Herzens*, K. A. von Bardenheub's Handbuch der Anatomie des Menschen, vol. 3, Part 1, Jena, 1913, Gustav Fischer.
16. Gross, L., and Kugel, M. A.: The Arterial Blood Vascular Distribution to the Left and Right Ventricles of the Human Heart, *AM. HEART J.* 9:165, 1933.
17. Robb, J. S.: The Structure of the Mammalian Ventricle, *M. Woman's J.* 41:65, 1934.
18. Gross, L.: *The Blood Supply of the Heart*, New York, 1921, Paul B. Hoeber, Inc.
19. Campbell, J. S.: Stereoscopic Radiography of the Coronary System, *Quart. J. Med.* 22:247, 1929.
20. Lower, R.: *Tractatus de Corde*. Translation by K. J. Franklin *In: Early Science in Oxford*, IX, Oxford, 1932, University Press, pp. 39, 82.

THE OCCURRENCE OF PAROXYSMAL HYPERTENSION IN PATIENTS WITH INTERMITTENT CLAUDICATION

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THE syndromes of angina pectoris and of intermittent claudication are similar in that both are dependent upon the activity of ischemic muscular organs. For this reason, the classical work of Lewis¹ and of Katz,² designed to elucidate the mechanism of angina pectoris, was done primarily on striated muscles since the arm or leg muscles lent themselves admirably for study. Exercise of muscles experimentally rendered ischemic* gives rise to: (1) pain within the region being exercised,^{3,4} (2) a marked increase in blood pressure,^{5,6} and (3) tachycardia.⁷ In spite of the fact that all three phenomena probably occur with the production of ischemia in muscles, only the pain element has been properly investigated.^{1-4,8-12} Incidental phenomena which occur in patients with intermittent claudication deserve an explanation. For example, hypertrophy of the heart without valvular disease was found by us in such patients, even though the blood pressure was normal at rest. The fact that many of these patients die suddenly without apparent cause also requires analysis.

In order to assay the possible clinical importance of the induced rise in blood pressure and the tachycardia, we have studied the general cardiovascular reactions produced by exercise of spontaneously ischemic voluntary muscles in man. In this report, the blood pressure changes and the variations produced by several drugs following exercise of the legs in patients with intermittent claudication are described. The observations concerned with heart rate and with the origin of the pain thus produced will be reported later.^{13,14} In addition, there is described a new method which permits the detection of impairment of the arterial circulation in exercising legs, even when the blood flow appears adequate at rest.

METHOD

Ten male patients, between the ages of 39 and 70 years, with intermittent claudication of the legs, were studied. Their clinical histories are summarized in Table I, A. The procedure described by Allen, Barker, and Hines¹⁵ was followed, but more stress was laid on oscillometry. For the purpose of this report we will deal only with the work of the posterior muscles of the leg, although it is recognized that other muscles of the body are also involved in the effort.

From the Pabellon de Cardiologia "Luis H. Inchausti," Hospital Ramos Mejia, Buenos Aires, Argentina.

Read before the Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, 1948.

*By ischemic muscles is meant muscles with a poor or an absent arterial blood flow.

A simple device, consisting essentially of two 4-kilogram weights which could be raised separately by each foot, was employed. The weights were raised 7.0 cm. at a rate of forty times a minute and the power developed by each leg was 11.2 kilogram-meters per minute. This is derived from the equation: Power = 4.0 Kilograms \times 0.07 meter \times 40 times per minute.

Patients were comfortably seated in a warm room fifteen to twenty minutes before starting the experiments. Blood pressures were determined by a cuff on the right arm every fifteen to twenty seconds, and the pulse rate was simultaneously recorded from the other arm. Each patient was then instructed to perform the exercise until he experienced pain similar to that noted in walking. After a rest, during which the pain disappeared, the exercise was repeated. The experiment was begun when the blood pressures and pulse rates had been constant for three successive minutes. The legs were exercised five times, first separately

TABLE I, A. CLINICAL STUDY OF PATIENTS WITH INTERMITTENT CLAUDICATION

PATIENT NO.	AGE	HEART FAILURE	ANGINA PECTORIS	HEART SIZE*	ELECTRO-CARDIOGRAM	DIABETES MELLITUS	EYE-GROUND CHANGES†	COLD-PRESSOR TEST ¹⁵	LOWER LIMBS‡	
									RIGHT	LEFT
1	51	Yes	No	Enlarged	Auric. fibr.	No	2	-	3	4
2	50	No	No	Normal	Normal	No	2	+	3	3
3	62	No	No	Normal	Normal	No	2	+	2	2
4	43	No	No	Enlarged	Normal	No	2	+	2	2
5	70	Yes	No	Enlarged	I-V block	No	-		2	2
6	39	No	No	Normal	Normal	No	2		2	1
7	62	No	No	Normal	Normal	No	2	+	3	3
8	45	No	No	Normal	Normal	Yes	-	+	3	2
9	50	Yes	Yes	Enlarged	C.C.I.	No	2	+	3	1
10	66	No	No	Normal	Normal	Yes	4	+	3	3

TABLE I, B. CLINICAL STUDY OF PATIENTS WITHOUT INTERMITTENT CLAUDICATION (CONTROLS)

PATIENT NO.	AGE	HEART FAILURE	ANGINA PECTORIS	HEART SIZE*	ELECTRO-CARDIOGRAM	CLINICAL DIAGNOSIS
11	42	No	No	Normal	Normal	Normal
12	20	No	No	Enlarged	L.V.P.	Coarctation of the aorta
13	16	No	No	Normal	Normal	Normal
14	66	No	No	Enlarged	L.V.P.	Rheumatic aortic stenosis
15	61	No	No	Enlarged	L.V.P.	Hypertensive heart disease

*Determined by x-ray examination.

†Classification of Wagener and Keith, *Medicine* 18:317, 1939.

‡1, Normal; 2, intermittent claudication in warm extremities; 3, intermittent claudication in cold extremities; 4, intermittent claudication in cold extremities, trophic changes and/or rest pain.

C.C.I., Chronic coronary insufficiency.

Auric. fibr., Auricular fibrillation.

I-V block, Intraventricular block.

L.V.P., Left ventricular preponderance.

and then both together. A ten-minute rest period was allowed between each limb exercise. If the patient experienced no pain, two ten-minute periods were studied, with a ten-minute rest period. Finally the same exercise was performed one minute after a pressure cuff inflated to 280 mm. Hg was placed around the thigh and continued until the appearance of pain similar to that experienced without the cuff.

As controls, five patients without intermittent claudication but with other cardiovascular disease (Table I,B) performed the same exercises.

RESULTS

Patients With Intermittent Claudication (Figs. 1-4).—In the ten patients exercise was performed unilaterally, seventy-four times; bilaterally, forty-seven times; and after the pressure cuff was placed around the thigh, seventeen times. In patients with unilateral intermittent claudication only, the results obtained in the diseased leg will be considered.

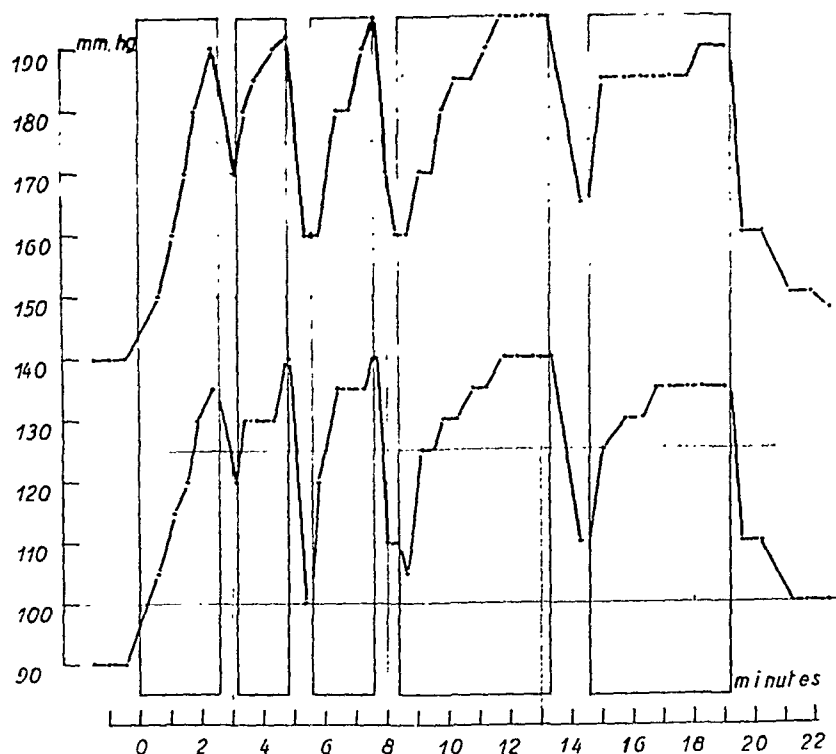


Fig. 1.—Typical experiment showing the blood pressure increases induced by unilateral leg exercise in Patient 8. The rectangles mark the exercising periods. (For method see text.) Upper line represents systolic and lower line represents diastolic pressure.

At the beginning of each exercise a sudden rise in blood pressure was observed which was sustained until the termination of the exercise; the blood pressure then returned toward the initial levels. The increase in pressure was not dependent on the development of pain, since the pressure always increased before pain appeared.

The blood pressure increases ranged between 0 and 70 mm. Hg and averaged 40 mm. systolic and 30 mm. diastolic. No significant difference in the pressure

increase was noted in patients during unilateral or bilateral exercise, with or without the induction of ischemia with the cuff. In two patients the pathologic process was unilateral. The systolic blood pressure increases brought about by the exercise of the diseased limb were between 30 and 60 mm. Hg, and the diastolic increases were between 30 and 45 mm. of mercury. The changes induced by the normal leg working under the same conditions were 5 to 20 mm. Hg systolic and 10 to 20 mm. Hg diastolic.

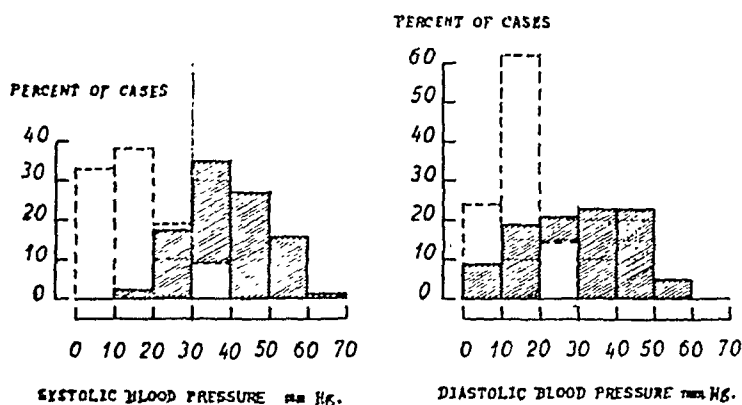


Fig. 4.—Frequency distribution of the blood pressure rises induced by the exercise of legs with intermittent claudication (solid gray rectangles), and of the legs of normal controls (dotted white rectangles).

The Ischemic Index (Fig. 5).—In order to compare the ischemia which occurs naturally with that induced artificially, the blood pressure variations induced by exercise were correlated by using the following formula:

$$I = \frac{\delta S + \delta D}{\Delta S + \Delta D}$$

in which

I = ischemic index,

δS = increase in systolic pressure during exercise without the cuff,

δD = increase in diastolic pressure during exercise without the cuff,

ΔS = increase in systolic pressure during exercise with the cuff, the exercise being continued until pain forced an end to the exercise, and

ΔD = increase in diastolic pressure during exercise with the cuff, the exercise being continued until pain forced an end to the exercise.

The ischemic index thus calculated was found to vary between 0.20 and 1.60, its mean value being 0.88 ± 0.03 and 1.01 ± 0.04 in unilateral and bilateral exercise, respectively. The difference between unilateral and bilateral exercise was not statistically significant. In 95 per cent of the cases the ischemic index was equal to or greater than 0.60.

Comment.—It is concluded that in our patients the same blood pressure variations were induced by exercising one leg, both legs together, or one leg with a

cuff that completely interrupted the arterial circulation. In other words, the same pressure increases could be induced with a partially ischemic limb (without the cuff) or with an absolutely ischemic limb (with the cuff). This finding cannot be applied to patients in whom the pathologic process was unilateral. In them, the blood pressure changes induced by exercising the healthy leg are smaller than those induced by exercising the diseased leg (Fig. 3), and the exercise of both together raises the pressure to levels similar to those induced by exercising the diseased limb alone.

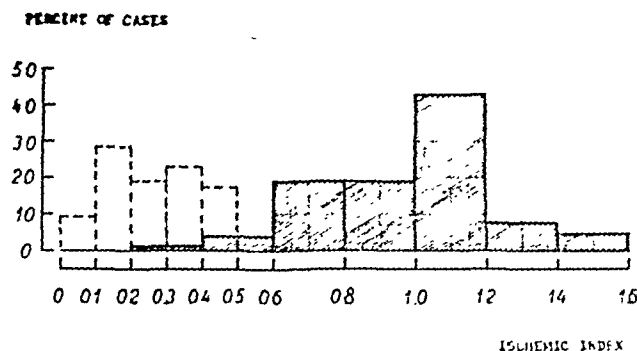


Fig. 5.—Frequency distribution of ischemic index in legs with intermittent claudication (solid gray rectangles), and in controls (dotted white rectangles).

Controls (Figs. 4 and 6).—The results obtained with the healthy leg in patients with unilateral intermittent claudication are also included here. In these seven patients, ten exercises were performed with both legs, twenty-one with one leg, and nine with one leg after the cuff was in place.

During the exercise of a nonischemic limb, the increase in blood pressure was very small, the maximum being registered from two to five minutes after the beginning of the exercise and returning toward the initial levels even before the exercise was completed. The blood pressure changes were found to lie between 0 and 40 mm. Hg, averaging 15.15 mm. Hg, regardless of whether one or both legs were exercised. The standard error of this difference¹⁷ is for the systolic pressure $\delta = 3.28$ and for the diastolic $\delta_D = 1.53$. These differences are therefore statistically insignificant, since they are smaller than twice these standard errors. The ischemic index was found to vary between 0 and 0.49, the mean being 0.26 ± 0.02 and 0.23 ± 0.03 in unilateral and bilateral exercises, respectively.

Comment.—It is concluded that in these patients with normal circulation to the limb, the same increase in blood pressure was produced by the exercise of one or of both legs, but greater differences were obtained when the exercise was performed under artificially induced ischemic conditions. Furthermore, it was generally found that the blood pressure fell toward normal even before the exercise was finished, although this never occurred in subjects with ischemic limbs. It is true that in subjects whose limbs were ischemic the exercising periods were shorter. The standard errors of the difference between the ischemic control and the nonischemic control limbs were 2.40 and 1.70 in the systolic and diastolic

pressures, respectively. As the difference between the means was much greater than twice these standard errors, the said difference is statistically significant.

The "ischemic index," which is easily determined, provides a valuable means for determining whether the arterial blood supply to the limb is adequate. It was found to be greater than 0.60 in 95 per cent of the patients with intermittent claudication and less than 0.50 in the patients without intermittent claudication.

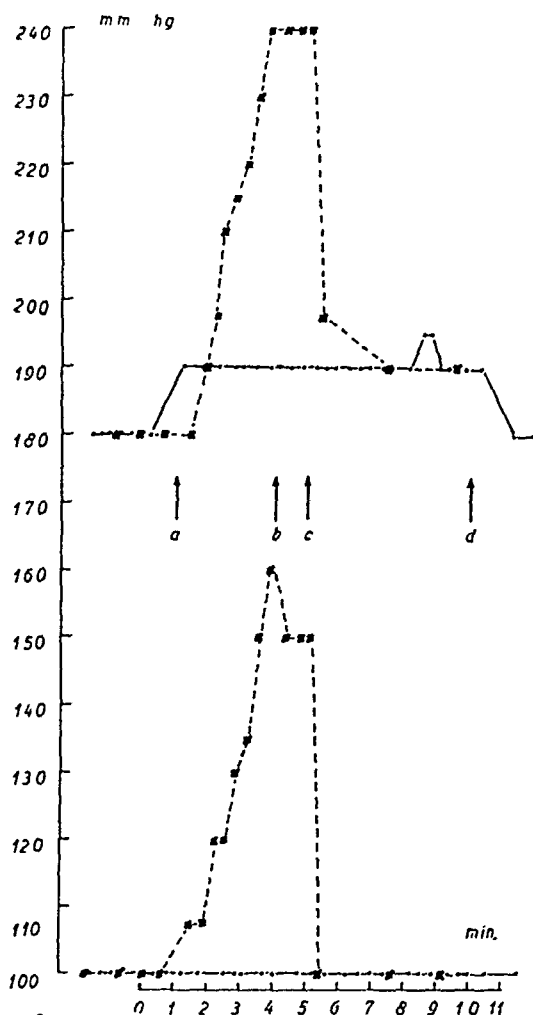


Fig. 6.—Blood pressure variations induced by leg exercise in a patient without intermittent claudication. This patient had coarctation of the aorta, but the arterial circulation in his legs was normal. The solid line represents systolic and diastolic blood pressures during exercise of the left leg without the cuff. The dotted line shows blood pressure during exercise of the same leg, but with a cuff inflated at 280 mm. Hg placed around the thigh. At *a* the same exercise was begun in both instances. In the experiment with the cuff (dotted lines) the exercise was stopped at *b*, but the cuff pressure was not released until *c*. In the experiment without the cuff, exercise began at *a* and continued until *d*. Note the great difference in blood pressure between the two experiments.

The Effect of Drugs on the Blood Pressure Rise in Patients With Intermittent Claudication.—In order to assay the mechanism of the pressor reaction, nitrites and tetraethyl ammonium chloride were used.

A. *Vasodilator Drugs* (Table II).—Nitrites, some with rapid action (nitroglycerine) and some with more prolonged effects (Mannitol hexanitrate), were given orally. In six patients, twenty-seven experiments were done five minutes

after the sublingual administration of four drops of an alcoholic nitroglycerine solution. As it was found that no differences existed between the pressor reaction induced by exercising one or both legs, these experiments will be jointly reported here. In five patients, the increases were smaller than when no nitroglycerine was administered; the systolic mean in all six patients was 23 ± 2 and the diastolic was 24 ± 3 mm. of mercury. The ischemic index was within normal limits in five patients and remained abnormally elevated in only one.

TABLE II. BLOOD PRESSURE VARIATIONS INDUCED BY LEG EXERCISE IN PATIENTS WITH INTERMITTENT CLAUDICATION, FOLLOWING THE ADMINISTRATION OF VASODILATOR DRUGS

INCREASE IN PRESSURE (MM. HG)	NUMBER OF OBSERVATIONS*			
	NITROGLYCERINE		MANNITOL HEXANITRATE	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
0-9	2	4	1	2
10-19	10	9	1	8
20-29	8	3	7	1
30-39	5	7	2	2
40-49	1	3	0	0
50-59	1	1	1	0
60-69	0	0	1	0
Total observations	27	27	13	13
Mean increase (in mm. Hg)	23	24	29	15
Standard error	± 2	± 3	± 4	± 2
Standard deviation	10	14	16	8

*Exercise of one or both legs is jointly reported here.

In two patients, the exercise was performed after the cuff inflated to a pressure of 280 mm. Hg was placed around the thigh. The blood pressure reactions in this case were similar to those produced without the nitroglycerine, the ischemic index being 0.93 and 1.28, respectively.

In four patients, thirteen bilateral exercises were performed one hour following the administration of Mannitol hexanitrates. The blood pressure changes were similar to those obtained without the drug, and in only six patients was the ischemic index found to be within normal limits.

It is concluded that nitroglycerine, a rapidly acting vasodilator, prevented the pressor reaction induced by the exercise of naturally occurring ischemic limbs, while Mannitol hexanitrates was only partially effective. Furthermore, the fact that nitroglycerine did not prevent the pressor reaction elicited after placing of the cuff suggests the presence of vascular spasm in some of these patients during exercise.

B. *Tetraethylammonium Chloride* (Table III).—In four patients, 0.7 to 1.2 Gm. of tetraethylammonium chloride were given intramuscularly one hour before the experiments. Fourteen experiments were performed with one leg, without the cuff, and four with one leg after the cuff was in place.

TABLE III. BLOOD PRESSURE VARIATIONS INDUCED BY LEG EXERCISE IN PATIENTS WITH INTERMITTENT CLAUDICATION, FOLLOWING THE ADMINISTRATION OF TETRAETHYLAMMONIUM CHLORIDE (TEA)

INCREASE IN PRESSURE (MM. Hg)	NUMBER OF OBSERVATIONS			
	EXERCISE ONE LEG			
	WITHOUT CUFF		WITH CUFF	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
0-9	1	1	0	0
10-19	6	7	1	1
20-29	5	4	1	1
30-39	1	1	1	1
40-49	0	1	0	1
50-59	0	0	1	0
60-69	1	0	0	0
Total observations	14	14	4	4
Mean increase (in mm. Hg)	22	20	32	30
Standard error	± 4	± 3	± 6	± 7
Standard deviation	14	10	11	13

In the exercise without the cuff, the increases ranged between 0 and 60 mm. Hg, with a systolic mean of 22 ± 4 and a diastolic mean of 20 ± 3 mm. of mercury. In the exercise with the cuff, the increases lay between 10 and 50 mm. Hg, with a systolic mean of 32 ± 6 and a diastolic mean of 30 ± 6 mm. of mercury. The ischemic index was less than 0.60 in ten cases.

It is concluded that although tetraethylammonium chloride blocks the autonomic ganglia, it did not suppress the pressor reaction of the exercise in our patients.

DISCUSSION

The values given by us for the blood pressure changes induced by the exercise in our control patients are different from those given by other authors for normal subjects.¹⁸⁻²¹ The apparent discrepancy can be accounted for by the differences in the methods employed, since the blood pressure changes are determined by the amount, the degree, and the duration of the exercise,²² being proportional, but not linearly so, to the work performed.²³ In our experience, similar blood pressure changes were induced with exercise of one or of both legs despite the fact that the work performed with two legs was twice as much as that performed with a single leg. The importance of recording the blood pressure *during* the exercise cannot be overemphasized, since the pressure rapidly returns to normal as soon as the exercise is stopped.^{20,24} In the majority of the control patients, the blood pressure tended to decrease after eight to ten minutes even though the exercise was continued. Similar observations have been reported by others.^{18,19} In contrast,

in our patients with intermittent claudication the hypertension was sustained during the entire exercising period. Postexertional hypotension was not seen by us, although this has been observed by others.²⁵

The effect of exercise of ischemic muscles has been studied clinically mainly from the point of view of the elicited pain,^{1-4,5-12} but few have investigated the arterial hypertension and tachycardia which occur coincidentally. Reid⁵ mentioned this fact, and Alam and Smirk^{6,7,26-28} and Malinow and his associates²⁹ made a nonstatistical study in patients without apparent arterial lesions. The hypertension induced by the exercise of ischemic muscles may belong to the "nutritive reflexes" of Hess,³⁰ which bring about an increase of blood pressure whenever an obstruction to the blood flow appears. This mechanism may be related to the rise in pressure brought about by ischemia of the kidney,³¹ of the uterus of pregnant dogs,³² of the heart,^{33,34} and by coarctation of the aorta and by the arterial injection of embolizing powder.³⁵

The physiopathology of pain in intermittent claudication has been exhaustively studied by Lewis¹ and by Katz,² and its clinicopathologic basis established mainly by Veal³⁶ and by Hines and Barker.³⁷ Nevertheless, the generalized blood pressure variations induced in patients with claudication by exercise of the legs have not been previously reported. Blood pressure changes similar to those described by us are mentioned by Thacker²⁵ during the exercise of hypertensive patients and may be induced by other mechanisms (emotions, cold, and so forth). Contrary to the findings of Alam and Smirk,²⁶ Hines³⁸ and Levy and associates³⁹ reported that marked blood pressure increases occur more often in subjects with a tendency to sustained hypertension; and Moscheowitz⁴⁰ and many others^{41,42} have stressed the role of hypertension in the production of arteriosclerosis. In our patients, great blood pressure variations were induced by exercise of the legs. While we cannot prove the importance of this mechanism in the development of hypertension or arteriosclerosis, there can be little doubt that these blood pressure changes must react unfavorably upon a previously damaged heart. In this connection, we should mention the coincidence of angina pectoris and intermittent claudication in Case 9.

The mechanism which we have reported may explain cardiac enlargement of unknown etiology in some patients. This is the case, we believe, in our 40-year-old patient (Case 8) without valvular lesions, with a normal electrocardiogram, and with x-ray signs of left ventricular enlargement. In this patient, while the resting blood pressure was 140/100 and 140/90, after a few seconds of leg exercise it increased to 190/140 (Fig. 1).

Sudden death is common in patients with intermittent claudication, but its cause has not been established.³⁷ The mechanism discussed in the present report, by producing repeated and sudden hypertension, may lead to cardiac or cerebral accidents in these patients. The mechanism of heart failure in patients with anemia or with generalized anoxia may also be related to the production of a rise in pressure on effort, with the resulting increased load on the heart.^{43,44} A pressor reaction in exercising ischemic muscles, without the occurrence of pain, was observed by us and will be reported elsewhere.¹⁴ In patients with angina pectoris, Levine³³ and Rosenbaum and associates³⁴ did not find a relationship between

pain and arterial hypertension. Our experience favors the same view, because (1) in some patients it was possible to obtain the pressor response without the occurrence of pain; (2) we frequently observed a decrease in blood pressure during the ischemic postexertional period, even in the face of persistent or increasing pain; and (3) tetraethylammonium chloride may suppress pain without completely abolishing the pressor response.

Although the hypertension was not abolished by tetraethylammonium chloride, there can be little doubt that it operates through a neurogenic mechanism.²⁶ This failure was due, probably, to incomplete block of the autonomic nervous system.⁴⁵⁻⁴⁷ A direct effect of an increased venous return can be eliminated in the pressor response brought about by the exercise of limbs with a cuff inflated at 280 mm. Hg and placed around the thigh. Our observations concerning the eradication of pain are in accord with what has been reported in cases of myocardial infarction,⁴⁸ in which pain is abolished in spite of the arterial hypotension occurring coincidentally with a probably secondary decrease in coronary flow.

Manifold procedures have been described in the clinical and instrumental study of vascular disorders in the limbs,^{16,49-55} but none of these measures the generalized reactions produced by the exercise of ischemic extremities. Our method is of value because it is simple and permits an easy recognition of ischemia during the exercise, a condition that occasionally may not be present at rest.

Vascular spasm has been repeatedly reported in patients with intermittent claudication.⁵⁶⁻⁶³ Our observations with nitroglycerine may support this view. We have found vasodilators to be of value in partially relieving the pressor reaction in intermittent claudication, and the local conditions may thereby be improved. The fact that vasodilators are not mentioned,⁶⁴⁻⁶⁷ or only incidentally mentioned,⁶⁸ in this connection, is due to the fact that the subjective phenomena are generally relieved in only a few cases.

CONCLUSIONS

In spite of the small number of observations, the following conclusions are tentatively offered:

1. The arterial hypertension induced by a standardized exercise of the legs in patients with intermittent claudication is much greater than that which occurs in patients without intermittent claudication. This hypertension, presumably also present while the patient is walking, represents a mechanism of repeated strain on the heart and may possibly be a determining factor in the production of arterial hypertension and/or arteriosclerosis, cardiac enlargement, and sudden death.

2. An ischemic index was found by comparison of the blood pressure changes induced by the aforementioned standardized exercises, before and after a pressure cuff inflated at 280 mm. Hg was placed around the thigh. This index was less than 0.50 in the control patients and greater than 0.60 in 95 per cent of the patients with intermittent claudication.

3. The pain experienced by these patients is apparently not the cause of the pressor response.

4. In spite of its accepted neurogenic mechanism, the pressor response was not completely abolished by tetraethylammonium chloride. In some patients it was partly abolished by vasodilator drugs, suggesting the presence of vascular spasm. The last-mentioned fact suggests that nitrites may be of value in the treatment of patients with intermittent claudication of the legs.

We wish to express our appreciation to Dr. L. N. Katz and Dr. S. Rodbard of Michael Reese Hospital, Chicago, for suggestions in the preparation of this manuscript.

REFERENCES

1. Lewis, T.: Pain in Muscular Ischemia. Its Relation to Anginal Pain, *Arch. Int. Med.* 49:713, 1932.
2. Katz, L. N.: Mechanism of Pain Production in Angina Pectoris, *AM. HEART J.* 10:322, 1935.
3. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, *Heart* 15:359, 1931.
4. Katz, L. N., Lindner, E., and Landt, H.: On the Nature of the Substance(s) Producing Pain in Contracting Skeletal Muscle: Its Bearing on the Problem of Angina Pectoris and Intermittent Claudication, *J. Clin. Investigation* 14:807, 1935.
5. Reid, C.: Experimental Ischemia: Sensory Phenomena, Fibrillary Twitchings and Effects on Pulse, Respiration and Blood Pressure, *Quart. J. Exper. Physiol.* 21:243, 1931.
6. Alam, M., and Smirk, F. H.: Observations in Man Upon a Blood Pressure Raising Reflex Arising From the Voluntary Muscles, *J. Physiol.* 89:372, 1937.
7. Alam, M., and Smirk, F. H.: Observations in Man on a Pulse-Accelerating Reflex From the Voluntary Muscles of the Legs, *J. Physiol.* 92:167, 1938.
8. MacWilliams, J. A., and Webster, W. J.: Some Applications of Physiology to Medicine. I. Sensory Phenomena Associated With Defective Blood Supply to Working Muscles, *Brit. M. J.* 1:51, 1923.
9. Perlow, S., Markle, P., and Katz, L. N.: Factors Involved in the Production of Skeletal Muscle Pain, *Arch. Int. Med.* 53:814, 1934.
10. Elliot, A. H., and Evans, R. A.: Ischemic Pain in Exercising Muscles: Its Nature and Implications, *AM. HEART J.* 12:674, 1936.
11. Maison, G. L.: Studies on the Genesis of Ischemic Pain: The Influence of the Potassium, Lactate and Ammonium Ions, *Am. J. Physiol.* 127:315, 1939.
12. Harpuder, K., and Stein, I. D.: Studies on the Nature of Pain Arising From an Ischemic Limb. II. Biochemical Studies, *AM. HEART J.* 25:438, 1943.
13. In preparation.
14. Malinow, M. R., Moia, B., Otero, E., and Rosenbaum, M.: Cambios Circulatorios Producidos en el Hombre por el Ejercicio de Musculos Isquemicos. II. Patogenia del Dolor en los Miembros Isquemicos. In preparation.
15. Hines, E. A., Jr., and Brown, G. E.: Cold Pressor Test for Measuring Reactibility of Pressure; Data Concerning 571 Normal and Hypertensive Subjects, *AM. HEART J.* 11:1, 1936.
16. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: *Peripheral Vascular Diseases*, Philadelphia, London, 1946, W. B. Saunders Company, pp. 32-65.
17. Hill, A. B.: *Principles of Medical Statistics*, London, 1948, The Lancet, Ltd., p. 112.
18. Bowen, W. P.: Changes in Heart Rate, Blood Pressure and Duration of Systole Resulting From Bicycling, *Am. J. Physiol.* 11:59, 1904.
19. Lowsley, O. S.: The Effects of Various Forms of Exercise on Systolic, Diastolic and Pulse Pressure and Pulse Rate, *Am. J. Physiol.* 27:446, 1911.
20. Paterson, W. D.: Circulatory and Respiratory Changes in Response to Muscular Exercise in Man, *J. Physiol.* 66:323, 1928.
21. Bock, A. V.: Studies in Muscular Activity. III. Dynamical Changes Occurring in Man at Work, *J. Physiol.* 66:136, 1928.
22. Steinhaus, H.: Chronic Effects of Exercise, *Physiol. Rev.* 13:103, 1933.
23. Gillespie, R. D., Gibbon, C. R., Jr., and Murray, D. S.: The Effect of Exercise on Pulse Rate and Blood Pressure, *Heart* 12:1, 1925.
24. Jacobson, E.: Variation of Blood Pressure With Brief Voluntary Muscular Contractions, *J. Lab. & Clin. Med.* 25:1029, 1940.
25. Thacker, E. A.: Blood Pressure Studies on University Students, Including the Effect of Exercise on Essential Hypertension, Hypotension and Normal Subjects, *Ann. Int. Med.* 14:415, 1940.

26. Alam, M., and Smirk, F. H.: Unilateral Loss of a Blood Pressure Raising, Pulse Accelerating, Reflex From Voluntary Muscles Due to a Lesion of the Spinal Cord, *Clin. Sc.* 3:247, 1938.
27. Alam, M., and Smirk, F. H.: Observations in Man Concerning the Effects of Different Types of Sensory Stimulation Upon the Blood Pressure, *Clin. Sc.* 3:253, 1938.
28. Alam, M., and Smirk, F. H.: Blood Pressure Raising Reflexes in Health, Essential Hypertension and Renal Hypertension, *Clin. Sc.* 3:259, 1938.
29. Malinow, M. R., Moia, B., Otero, E., and Garcia, A.: Cambios Circulatorios Producidos en el Hombre por el Ejercicio de Musculos Isquemicos. I. Observaciones Preliminares, *Rev. argent. de cardiol.* 15:1, 1947.
30. Hess, W. R.: Die Functionen des vegetatives Nervensystems, *Klin. Wchnschr.* 9:1009, 1930.
31. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* 59:347, 1934.
32. Ogden, E., Hildebrand, G. J., and Page, E. W.: Rise of Blood Pressure During Ischemia of the Gravid Uterus, *Proc. Soc. Exper. Biol. & Med.* 43:49, 1940.
33. Levine, S. A., and Ernestene, A. C.: Observations on Arterial Blood Pressure During Attacks of Angina Pectoris, *AM. HEART J.* 8:323, 1932.
34. Rosenbaum, M., Moia, B., Otero, E., Skibinsky, J., and Malinow, M. R.: Varaciones de la Presion Arterial Durante el Ejercicio Muscular en Sujetos Anginosos. In preparation.
35. Tournade, A., and Rocchisani, L.: Mechanisme des effets hypertenseurs qu'engendre l'injection de poudre embolisante dans l'artere principale d'un membre, chez le chien, *Compt. rend. Soc. de. biol.* 116:203, 1934.
36. Veal, J. R.: The Pathological Basis for Intermittent Claudication in Arteriosclerosis, *AM. HEART J.* 14:442, 1937.
37. Hines, E. A., Jr., and Barker, N. W.: Arteriosclerosis Obliterans: A Clinical and Pathological Study, *Am. J. M. Sc.* 200:717, 1940.
38. Hines, E. A., Jr.: Range of Normal Blood Pressure and Subsequent Development of Hypertension. A Follow-up Study of 1522 Patients, *J. A. M. A.* 115:271, 1940.
39. Levy, R. L., White, P. D., Stroud, W. D., and Hillman, C. C.: Sustained Hypertension. Predisposing Factors and Causes of Disability and Death, *J. A. M. A.* 135:77, 1947.
40. Moschcowitz, E.: Vascular Sclerosis With Special Reference to Arteriosclerosis, New York 1942, Oxford University Press.
41. Rosenthal, S. R.: Studies in Atherosclerosis: Chemical, Experimental and Morphological, Role of Blood Pressure, *Arch. Path.* 18:660, 1934.
42. Andrus, F. C.: Relation of Age and Hypertension to Structure of Small Arteries and Arterioles in Skeletal Muscle, *Am. J. Path.* 12:635, 1936.
43. Pickering, G. W., and Wayne, E. J.: Observations on Angina Pectoris and Intermittent Claudication in Anemia, *Clin. Sc.* 1:305, 1934.
44. Kissin, M.: The Production of Pain in Exercising Muscle During Induced Anoxemia, *J. Clin. Investigation* 13:37, 1934.
45. Acheson, G. H., and Moe, G. K.: Some Effects of Tetraethyl Ammonium Chloride on the Mammalian Heart, *J. Pharmacol. & Exper. Therap.* 84:189, 1945.
46. Acheson, G. H., and Moe, G. K.: The Action of Tetraethyl Ammonium Ion on the Mammalian Circulation, *J. Pharmacol. & Exper. Therap.* 87:220, 1946.
47. Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, G. K., and Sutter, M. L.: The Use of Tetraethyl Ammonium in Peripheral Vascular Disease and Causalgic States: A New Method for Producing Blockade of the Autonomic Ganglia, *Surgery*, 20:525, 1946.
48. Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man With Tetraethyl Ammonium, *Am. J. M. Sc.* 213:315, 1947.
49. Pickering, G. W.: On Clinical Recognition of Structural Disease of Peripheral Vessels, *Brit. M. J.* 2:1106, 1933.
50. Hitzrot, L. H., Naide, M., and Landis, E. M.: Intermittent Claudication Studied by a Graphic Method, *AM. HEART J.* 11:513, 1936.
51. Simmonds, H. T.: Intermittent Claudication and Its Quantitative Measurement, *Lancet* 1:73, 1936.
52. Kramer, L. I.: Various Methods of Determining the Early Diagnosis of Arteriosclerosis in Diabetes, *New England J. Med.* 220:278, 1939.
53. Montgomery, M., Naide, M., and Freeman, N. E.: The Significance of Diagnostic Tests in the Study of Peripheral Vascular Diseases, *AM. HEART J.* 21:780, 1941.
54. Landowne, M., and Katz, L. N.: A Critique of the Plethysmographic Method of Measuring Blood Flow in the Extremities of Man, *AM. HEART J.* 25:644, 1942.
55. Abramson, D. I.: Vascular Responses in the Extremities of Man in Health and Disease, Chicago, 1944, University of Chicago Press, pp. 28-80.
56. Comroe, J. H.: Paroxysmal Angiospasm Dolorosa, *Ann. Clin. Med.* 1:313, 1923.

57. Thomas, A.: L'Angiospasme provoqué dans les artérites périphériques et la claudication intermittente, *Préssé méd.* **2**:1049, 1922.
58. Pearl, F. L.: Angiospastic Claudication, With Report of Six Cases, *Am. J. M. Sc.* **191**:505, 1937.
59. Leary, W. V., and Allen, E. A.: Intermittent Claudication as a Result of Arterial Spasm Induced by Walking, *AM. HEART J.* **22**:719, 1941.
60. Freeman, N. E., and Montgomery, H.: Lumbar Sympathectomy in the Treatment of Intermittent Claudication; Selection of Cases by Claudication Tests With Lumbar Paravertebral Procaine Injection, *AM. HEART J.* **23**:224, 1942.
61. Lindqvist, T.: Intermittent Claudication and Vascular Spasm. I. Is Vascular Spasm a Contributory Cause of Intermittent Claudication in Patients With Structural Disease of the Arteries? *Acta med. Scandinav.* **121**:32, 1945.
62. Lindqvist, T.: Intermittent Claudication and Vascular Spasm. II. Can Intermittent Claudication be Due to Vascular Spasm Without Accompanying Structural Disease of the Arteries? *Acta med. Scandinav.* **121**:409, 1945.
63. Ejrup, B.: Tonoscillography After Exercise in Peripheral Vascular Disease and Coarctation of the Aorta, *AM. HEART J.* **35**:41, 1948.
64. McKittrick, L. S.: The Diagnosis and Management of Chronic Obliterative Vascular Disease, *J. A. M. A.* **113**:1223, 1939.
65. Herrman, L. G., and Reid, M. R.: The Conservative Treatment of Arteriosclerotic Peripheral Vascular Disease, *Ann. Surg.* **100**:750, 1934.
66. Smithwick, R. H., and White, J. C.: Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, *Surg., Gynec. & Obst.* **60**:1106, 1935.
67. Collens, W. S., and Wilensky, N. D.: Intermittent Venous Occlusion in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* **109**:2125, 1937.
68. Wright, I. S.: The Treatment of Arteriosclerosis Obliterans; Social Significance and Ultimate Objective, *J. A. M. A.* **115**:893, 1940.

THE ROLE OF ANEMIA IN THE EXPERIMENTAL PRODUCTION OF HEART BLOCK AND AURICULAR FIBRILLATION IN THE DOG

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TWO factors seem principally involved in the pathogenesis of auricular fibrillation in man and animals. The role of the vagus in the experimental production of auricular fibrillation has been established by numerous observers. Auricular fibrillation has been produced in animals and in man by the injection of parasympathomimetic substances, and in the dog by the simultaneous electrical stimulation of the vagus nerves and the auricles faradically. The second important etiological factor is anoxia of the heart. In the department from which this paper comes, Schlichter,¹ who has recently observed the development of auricular fibrillation in certain cases of anemia in man and its disappearance after transfusion, has emphasized the importance of anemia. The present investigation was undertaken in an attempt to evaluate further the role of anemia in the production of cardiac conduction disturbances as well as auricular fibrillation.

METHODS

A total of thirty-three dogs was employed in this study. Twenty-seven experiments with anemia, involving twenty-one dogs, were successfully completed. In seventeen experiments the dogs were anesthetized with Nembutal (25 mg. per kilogram), and in ten experiments unanesthetized trained dogs were used. Examination of the results with anesthetized and unanesthetized dogs revealed little difference in the reactions obtained. Standardization procedures conducted before and after anesthesia revealed little difference in the minimal standardizing dose of acetylcholine required.

Anemia was produced by three separate methods. Five animals were used twice each for the induction of anemia by different methods, and in one animal anemia was induced twice by the same method. In thirteen experiments in twelve dogs, anemia was produced by acetylphenylhydrazine given intramuscularly in dosage of 60 to 125 mg. per kilogram, divided into three daily doses. Eight dogs were made anemic by being fed *n*-propyl disulfide, 1.0 c.c. daily for four to six days. In six experiments anemia was produced by daily puncture of

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This department is supported in part by the Michael Reese Research Foundation.

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the femoral artery and removal of blood by means of a vacuum bottle. Hemoglobin determinations were made by the photocolorimetric method at the time of standardization procedures.*

Acetylcholine chloride† was employed‡ for the production of cardiac arrhythmias. The drug was dissolved in distilled water in concentrations of 0.1 mg. per cubic centimeter, 1.0 mg. per cubic centimeter, and 10.0 mg. per cubic centimeter, and injected into the right foreleg vein of the dog. Injections were always made into the same area of the vein in order to eliminate differences in circulation time. Electrocardiographic tracings were taken by means of a direct-writing electrocardiograph (Viso-Cardiette). Varying amounts of acetylcholine in volumes not larger than 1.0 c.c. were injected as rapidly as possible with a tuberculin syringe and a No. 23 needle until the minimal dose which would produce second degree A-V block was determined. At least three minutes were allowed to elapse between successive injections. In most instances a single blocked-out ventricular beat constituted the response to the minimal dose. In all instances, before the establishment of the minimal dose, a slightly smaller dose was injected at least twice, and shown to be incapable of producing second degree A-V block. After the establishment of the minimal dose,‡ doses of ten and twenty times this amount were injected. The standardization procedure was repeated two and occasionally three times on different days, the intervals varying from days to weeks. After the animals had been properly standardized, anemia was produced by the methods described and the standardizations were repeated with the animals at various levels of anemia, both in the stage of increasing anemia and in the recovery stage.

RESULTS

1. *Minimal Standardizing Dose of Acetylcholine.*—It was found that the control minimal standardizing dose necessary to produce second degree A-V block showed wide variability among different animals, ranging from 0.08 mg. to 3.0 mg. of acetylcholine. However, the control minimal standardizing dose for any individual animal remained relatively constant even when the determinations were separated by many weeks. This is well illustrated in Table V. The minimal standardizing dose did not appear to be related to the weight or sex of the animals, but did show a crude relationship to the animals' initial hemoglobin levels (Fig. 1). A given weight of acetylcholine produced a similar effect regardless of the dilution of the solution employed. This constancy of response to acetylcholine provided us with a base line for the determination of changes in sensitivity to the production of A-V block and auricular fibrillation. Anemia produced by any of the three methods employed resulted in increased sensitivity of the animals to acetylcholine. Block and auricular fibrillation were produced by doses of acetylcholine much smaller than those required in the pre-anemia

*We are indebted to Dr. K. Singer, Hematology Department, for his kindness in permitting us to use his photocolorimeter.

†We are indebted to Hoffmann-LaRoche, Inc., for the generous supply of this drug.

‡Henceforth referred to as the "minimal standardizing dose."

standardizations. After the animals had recovered from the anemia, the minimal standardizing dose returned in most instances to levels comparable with the pre-anemia standardizations.

ALL STARTING M.S.D. GRAPHED AGAINST HGB.

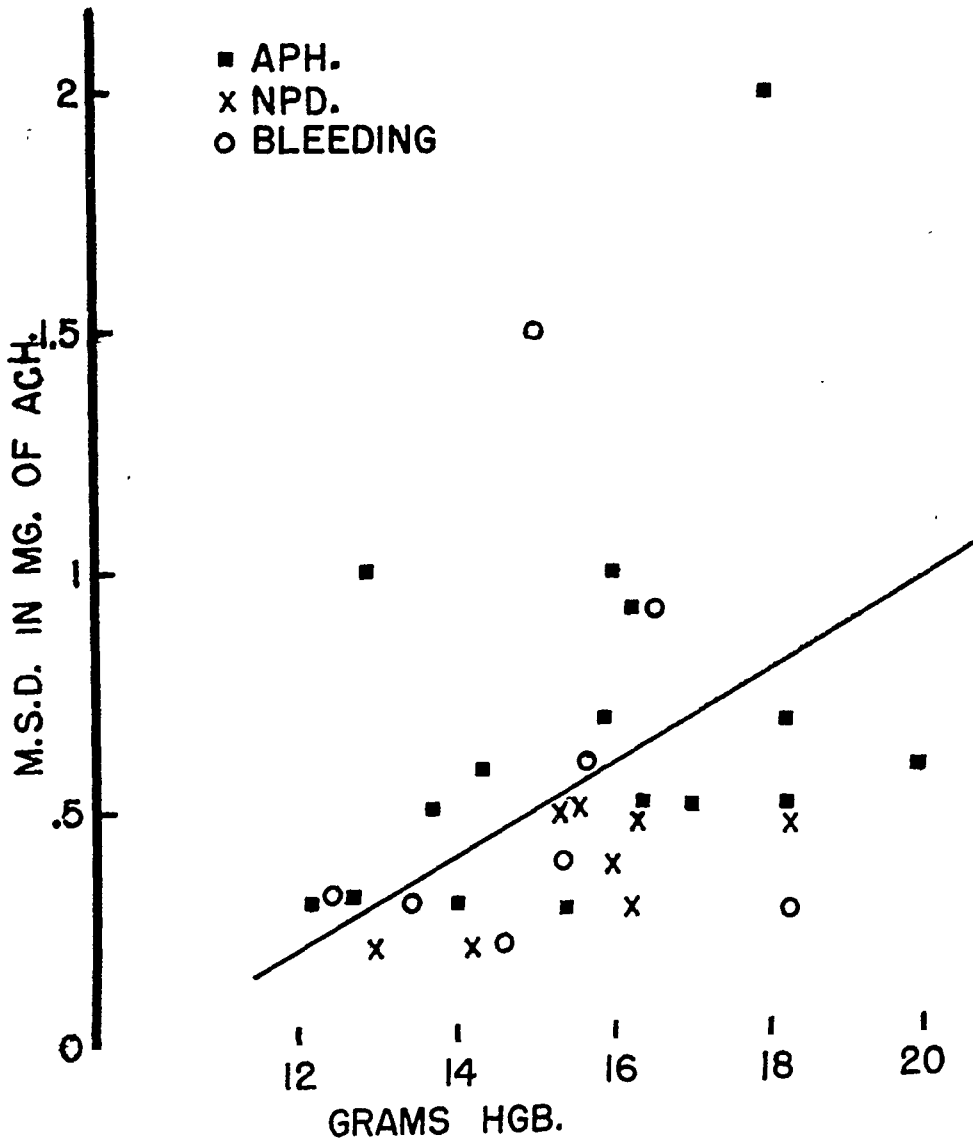


Fig. 1.—Relation between starting minimal standardizing dose (M.S.D.) of acetylcholine and hemoglobin content (Hgb) of blood. APH = acetylphenylhydrazine dogs; NPD = *n*-propyl disulfide dogs; bleeding = dogs in which hemorrhagic anemia was produced; ACH. = acetylcholine.

2. *Effects of Acetylphenylhydrazine (APH) Anemia.*—Thirteen experiments (in twelve dogs) were performed. One dog was used twice with a six-month intervening period. The first evidence of a fall in hemoglobin occurred on the day following the first injection of acetylphenylhydrazine. During the next two days, when this drug was still being given, continued small falls in hemoglobin occurred. Between the third and tenth day following the initial injection there was a precipitous fall in the hemoglobin level, the low point being reached within

three to seven days of the third injection. In some animals the fall in hemoglobin continued and the animal died. With the doses of acetylphenylhydrazine employed by us the low point of hemoglobin appeared to be in the neighborhood of 9.0 grams per cent. The animals which subsequently recovered attained normal hemoglobin levels in two to four weeks after the low point had been reached. In every instance in which anemia was produced by this method, the animals became markedly sensitive to the production of heart block, with the minimal standardizing dose falling to levels of approximately 10 per cent of the control values. Sensitivity was greatest when the anemia was most marked. In those animals which were followed closely during the early stages of the de-

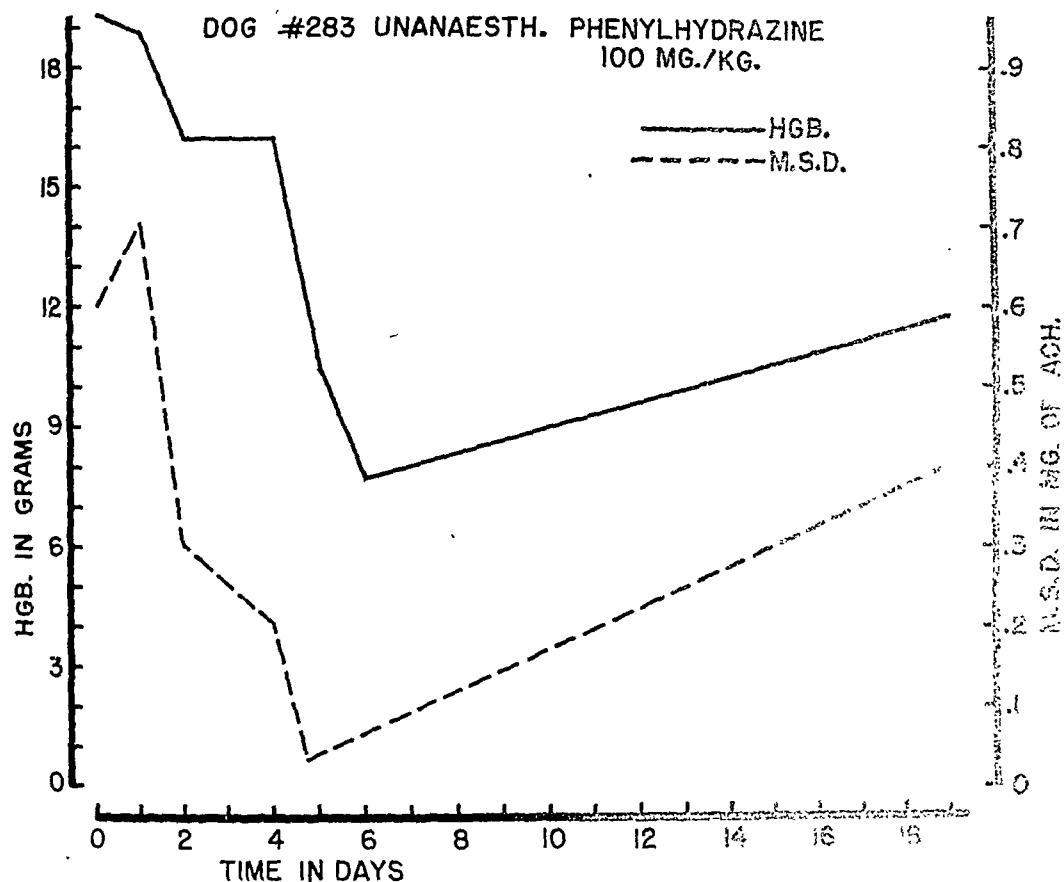


Fig. 2.—Typical experiment with phenylhydrazine. Symbols as in Fig. 1.

veloping anemia, it could be seen that within twenty-four hours after the injection of the initial dose of acetylphenylhydrazine, sensitivity began to increase considerably, although the hemoglobin levels had fallen only slightly. Sensitivity continued to increase with the fall in the hemoglobin levels and reached its maximum at the lowest hemoglobin levels. As the animals were allowed to recover from the anemia, the sensitivity decreased and the minimal standardizing dose eventually returned to levels approximating those of the control values. Fig. 2 shows the parallelism between the hemoglobin levels and the minimal standardizing dose in a representative dog. Results obtained in all dogs treated with acetylphenylhydrazine and surviving sufficiently long are tabulated in Table 1.

TABLE I. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE BEFORE AND AFTER ACETYLPHENYLHYDRAZINE (APH) ANEMIA

DOG NO.	BEFORE APH		AFTER APH	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
0362	14.3	0.5 0.6 0.6	5.7 13.0	0.09 0.6
9268	18.1	2.0 2.5	4.4 11.1	0.2 1.0
9753	12.7	0.4 1.0 1.0 0.9	5.7 8.1 14.2	0.1 0.5 0.7
9121	16.3	0.9 0.9	5.6 14.7 16.7	0.05 0.6 0.4
202	18.2	0.4 0.5	16.8 9.4 5.3 8.8 11.2	0.1 0.1 0.05 0.3 0.5
196	14.0	0.3 0.3	11.1 6.6 6.1 13.4	0.1 0.02 0.05 0.2
165	15.9	0.7 0.6	5.1 12.3 13.8	0.1 0.7 0.2
9843	12.2	0.3	9.5 15.6	0.1 0.5
0347	14.6	0.2 0.2	5.5 4.0	0.02 0.01
0362	18.2	0.7	16.6 14.5 13.1 4.6	0.7 0.4 0.2 0.06
283	19.9* 15.4*	0.6 0.2 0.4	19.4 16.3 16.3 7.8 11.6	0.7 0.5 0.3 0.2 0.05 0.4

Hgb. = hemoglobin.

*Values from a previous experiment. See Table II.

3. *Effects of Hemorrhagic Anemia.*—Six dogs were standardized for this procedure. Usually a marked anemia was produced in three to five days. All six dogs were followed into the anemic phase, and there was a definite increase

in sensitivity to acetylcholine as judged by the development of second degree A-V block. Two dogs were maintained in a severely anemic state for approximately two weeks, and continued during this period to display a marked sensitivity to the development of A-V block. In the four dogs which recovered completely from the anemia, as the hemoglobin values rose there was a decline of the sensitivity toward pre-anemia levels. The sensitivity which developed during the hemorrhagic anemia was at its peak when the anemia was most severe. The sensitivity was not, however, so great as that which developed following the use of acetylphenylhydrazine. Results of the experiments with hemorrhage are summarized in Table II, and a representative curve is shown in Fig. 3.

TABLE II. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE BEFORE AND AFTER HEMORRHAGIC ANEMIA

DOG NO.	BEFORE HEMORRHAGE		AFTER HEMORRHAGE	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
282	13.5	0.3	9.5	0.2
		0.3	6.3	0.1 0.1
202	18.2	0.3	10.4	0.05
	18.2*	0.4		
	18.2	0.5		
9753	16.8	0.9	10.5	0.15
	12.7*	1.0	8.4	0.20
		1.0	7.0	0.08
		0.9	4.9	0.15
			7.1	0.15
			7.0	0.1
			11.2	0.5
			12.4	0.6
0490	12.5	0.3	5.5	0.05
	16.4*	0.3	7.1	0.09
			5.8	0.07
			8.4	0.2
			10.2	0.1
267	14.9	1.0	10.3	0.8
		1.5	7.5	0.4
		2.0	8.6	0.4
			6.3	0.4
			7.0	0.5
			12.4	1.0
283	15.4	0.2	12.7	0.2
		0.4	9.5	0.2
			6.3	0.075
			8.8	0.1
			7.9	0.2
			11.9	0.5

Hgb. = hemoglobin.

*Values from a previous experiment. See Table I.

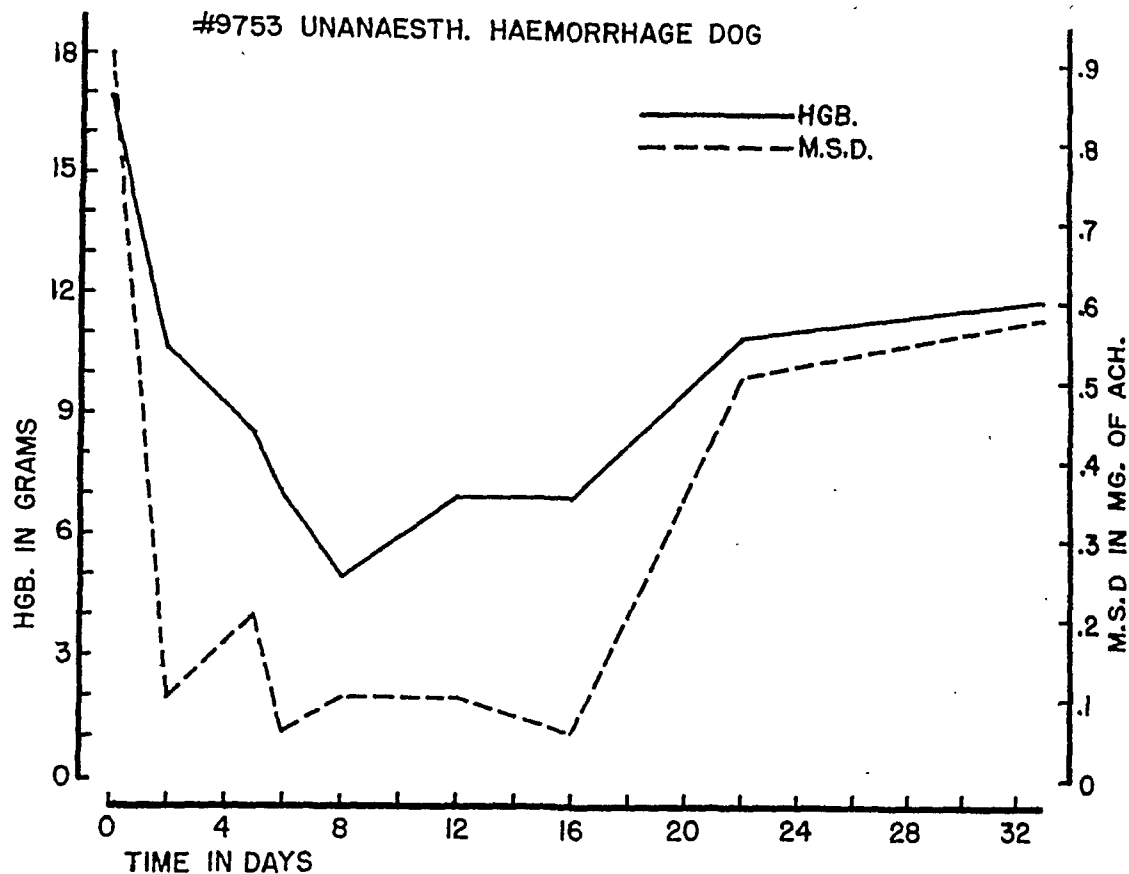


Fig. 3.—Typical experiment with hemorrhage. Symbols as in Fig. 1.

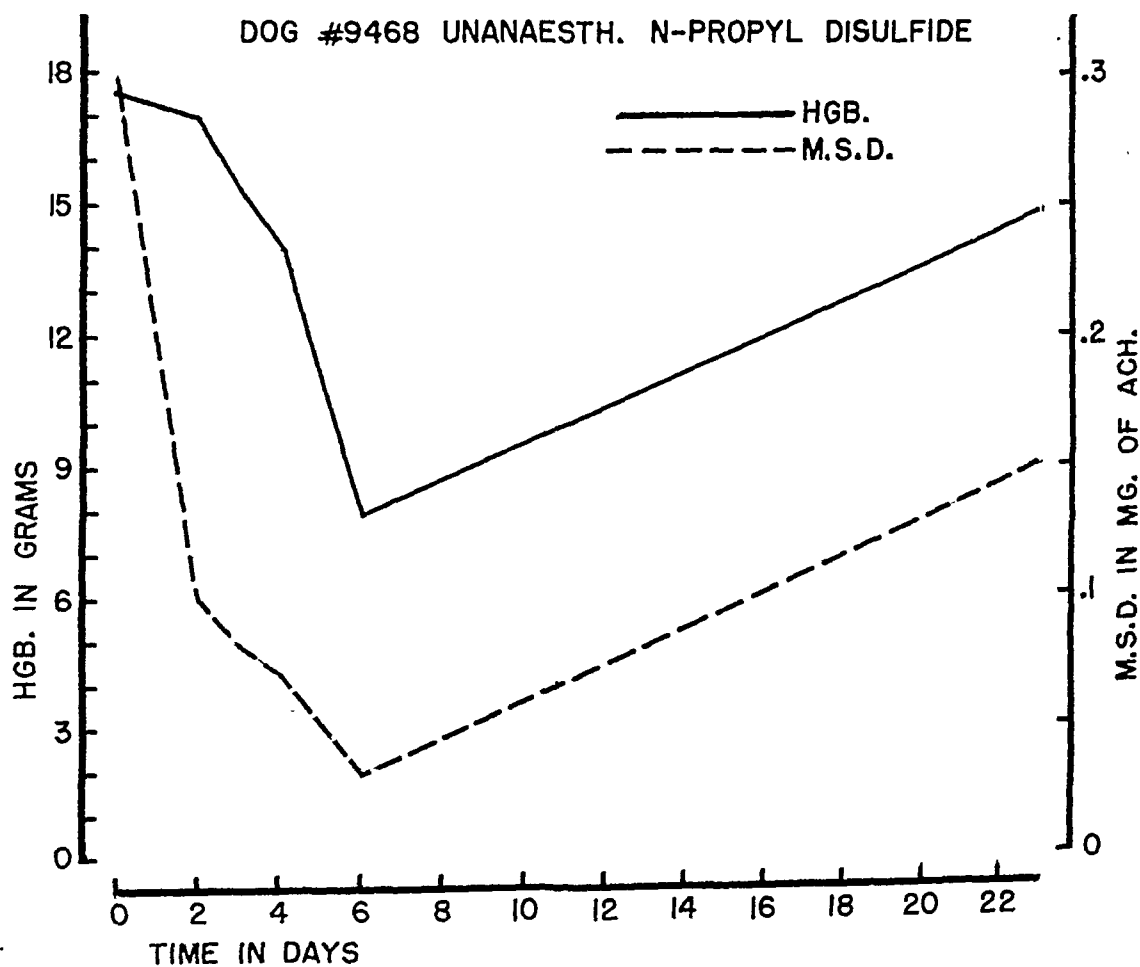


Fig. 4.—Typical experiment with *n*-propyl disulfide. Symbols as in Fig. 1.

4. *Effects of n-Propyl Disulfide Anemia.*—Eight dogs were standardized for this procedure. Five dogs showed a lowered minimal standardizing dose when assayed with acetylcholine during the anemic phase. As in the other types of anemia, the maximum sensitivity occurred at the lowest hemoglobin levels. The order of increased sensitivity during this anemia was about five times, as compared with ten times following acetylphenylhydrazine. A representative positive response in one animal is shown in Fig. 4, and the results in all animals are tabulated in Table III.

TABLE III. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE IN PRODUCING AURICULAR FIBRILLATION BEFORE AND AFTER *n*-PROPYL DISULFIDE (NPD) ANEMIA

DOG NO.	BEFORE NPD		AFTER NPD	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
0489		0.4	7.1	0.1
	13.2	0.4	4.6	0.3
	15.4	0.5	4.6	0.3
				0.4
			6.6	0.4
			10.1	0.8
0490	16.4	0.3	6.6	0.2
	12.5*	0.3	6.9	0.2
0454	18.3	0.5	9.5	0.2
	16.7	0.2	6.6	0.2
	16.7	0.3	8.5	0.2
			8.7	0.3
			10.6	0.3
9468	17.4	3.0	16.7	0.1
	18.1	2.0	15.1	0.8
			14.0	0.7
	18.1	2.5	7.9	0.2
0607		0.4	4.9	0.08
	16.1	0.4		
		0.3	13.0	0.4
0612		0.5	8.4	0.1
	16.1	0.4	15.0	0.5
0603		0.2	4.2	0.05
		0.1	12.2	0.1
	13.0	0.2		
0619		0.3	7.9	0.08
	15.3	0.9	13.7	0.3
		0.5		

Hgb. = hemoglobin.

*Values from a previous experiment. See Table II.

5. *Auricular Fibrillation.*—We observed a marked individual variation among dogs with respect to the ease with which auricular fibrillation could be induced by acetylcholine. Fifty per cent of all dogs tested fibrillated at some time or other in the pre-anemic stage. Our results are condensed in Table IV,

TABLE IV. INCREASED TENDENCY TO AURICULAR FIBRILLATION DURING ANEMIA

GROUP	APH	HEM	NPD
Never fibrillated	6(4)	3(1)	2(1)
Occasionally fibrillated	4(2)	2(2)	4(1)
Consistently fibrillated	2(0)	1(0)	2(2)

APH = acetylphenylhydrazine anemia.

HEM = hemorrhagic anemia.

NPD = *n*-propyl disulfide anemia.

Figures outside parentheses show the number of animals in the group; figures in parentheses show the number of animals which showed increased tendency to fibrillation of auricles after development of anemia, or which required less acetylcholine to lead to auricular fibrillation.

in which the animals carried completely through all phases of the anemias are divided into three groups according to whether the animal in the pre-anemic state (a) never fibrillated, (b) occasionally fibrillated, or (c) consistently fibrillated. The numbers enclosed within parentheses indicate the number of animals in the same group, which, after the induction of anemia, showed an increased tendency to fibrillate, fibrillation developing either more frequently or with smaller doses of acetylcholine. As can be seen, of eleven dogs which had never fibrillated before anemia, six fibrillated during the anemic phase. While the sensitization to fibrillation is difficult to discern in some animals because of the absence of a minimal fibrillating dose, it is clear and unmistakable in others. A record of one of the latter animals is shown in Table V. It should be clearly realized that

TABLE V. RELATION OF MINIMAL STANDARDIZING DOSE OF ACETYLCHOLINE REQUIRED TO PRODUCE AURICULAR FIBRILLATION TO HEMOGLOBIN CONTENT OF BLOOD IN A TYPICAL EXPERIMENT

DATE	HGB. (GM.)	MSD (MG.)
2/28/48	15.2	0.3
3/ 5/48		0.3
3/19/48		0.4
3/26/48		0.4
4/ 9/48		0.5
5/11/48		0.3
5/15/48	14.1	0.4
5/20/48		0.3
6/ 4/48		0.1
6/ 7/48		0.02
6/ 9/48		0.02

Hgb. = hemoglobin.

MSD = minimal standardizing dose.

there is no minimal dose of acetylcholine which can properly be called a "minimal fibrillating dose," since the production of fibrillation is largely dependent upon the location and timing of the initial impulse leading into fibrillation. It follows, therefore, that fibrillation may follow the administration of a given dose of acetylcholine but shortly thereafter may not follow the administration of the same or a larger dose.

6. *Relationship Between Supraventricular Block and the Development of Auricular Fibrillation.*—When electrocardiographic records showing the development of auricular fibrillation were examined, in almost all cases it was found that a P wave blocked from transmission to the ventricles immediately preceded the onset of the fibrillatory waves and seemed to initiate them. This phenomenon appears in other published tracings²⁻⁵ but has been insufficiently emphasized except by two groups of authors.^{4,5} In many of our tracings in which there was A-V block, there were P waves of unusual contour during the period of block. These P waves may be described as "double P waves" or polyphasic auricular waves. On a number of occasions it was these peculiar auricular waves which led into the typical *f* waves of auricular fibrillation. These multiple auricular waves probably represent re-entry within the auricles of an impulse arising in the sinus node or the auricles. We are in accord, therefore, with the previous deduction on this point reported from this department.⁶

7. *Relationship of Dose of Acetylcholine to the Length of Auricular Fibrillation.*—In dogs which fibrillated consistently, we observed a crude relationship between the dose of acetylcholine administered on a given day, and the length of time during which the auricles fibrillated following that dose. The figures listed in Table VI illustrate this relationship and show that with increasing doses

TABLE VI. RELATIONSHIP OF DOSE OF ACETYLCHOLINE TO DURATION OF AURICULAR FIBRILLATION IN THREE REPRESENTATIVE DOGS

DOG NO.	HGB. (GM.)	ACETYLCHOLINE (MG.)	DURATION OF AURICULAR FIBRILLATION (SECONDS)
9753	7.0	0.8	29
		1.6	53
		1.5	19
	7.1	3.0	100
		1.0	36
		2.0	99
0489	13.2	4.0	33
	15.4	8.0	84
		5.0	48
		10.0	49
	7.1	0.1	27
		1.0	40
		2.0	60
	4.6	3.0	90
		6.0	116
		3.0	44
	4.6	6.0	56
		4.0	29
		8.0	40
	14.2	5.0	30
		10.0	27
9810	14.3	0.2	17
		0.4	22
		2.0	32
		4.0	48
		6.0	3
	14.3	6.0	76
		0.5	23
		1.0	44
		2.0	145

Hgb. = hemoglobin.

of acetylcholine there is increased length of the period of fibrillation. There was a similar relationship between the dose of acetylcholine and the length of time during which the A-V block persisted. This latter relationship, which was clear when no fibrillation was seen, could also be observed when auricular fibrillation was present. In all cases where auricular fibrillation was produced, the high grade of block initially produced was manifested by a slow ventricular rate at the onset of fibrillation. As the period of fibrillation progressed, the ventricular rate increased markedly, indicating a lessening and disappearance of the A-V block. To investigate this relationship in greater detail we used an intravenous infusion of acetylcholine, in three instances, to produce and maintain auricular fibrillation over long periods of time. We observed that once auricular fibrillation was initiated, we could control the rate of transmission of impulses from auricles to ventricles by increasing or decreasing the rate of flow of the infusion. Data on such an experiment are presented in Table VII. It is clear that with higher rates of flow the ventricular rate was definitely depressed. In such a preparation, if the rate of flow of the infusion is slowed below a certain critical level for the animal, auricular fibrillation will cease after a variable period and give way to sinus rhythm. Auricular fibrillation can be reinitiated by once again speeding up the rate of the infusion. We have observed auricular fibrillation to continue for as long as sixty minutes after the cessation of the infusion.

TABLE VII. RELATIONSHIP OF RATE OF ACETYLCHOLINE INFUSION TO AVERAGE VENTRICULAR RATE IN AURICULAR FIBRILLATION IN ONE DOG (No. 9810)

ACETYLCHOLINE (DROPS PER MINUTE)	INFUSION (MG. PER MINUTE)	AVERAGE VENTRICULAR RATE (PER MINUTE)
52	7.4	80
30	4.0	116
18	2.0	150
12	1.75	170
112	16.0	33

8. *Observations Regarding the Spontaneous Termination of Auricular Fibrillation.*—The longest period of auricular fibrillation produced by a single rapid injection of acetylcholine was nine and one-half minutes. Auricular fibrillation, when produced, proceeded in the following manner: There was an increase in the ventricular rate as the fibrillation continued, until the ventricular rate stabilized itself at a rate of the order of 300 per minute. Spontaneous reversion to sinus rhythm was preceded by a pause which was always longer than the preceding cycle length. This pause was followed by the appearance of a regular ventricular rate, each QRS complex being preceded by a P wave. On several occasions we observed a transition from auricular fibrillation to auricular flutter, both pure and impure. On one occasion, following a single injection of 1.0 mg. of acetylcholine, auricular fibrillation ensued, with progression into pure flutter, which lasted for forty-three minutes and finally reverted to sinus rhythm. Reappearance of sinus rhythm is frequently preceded by slowing and increased amplitude of the *f* waves (coarse auricular fibrillation).

9. *Electrocardiographic Changes*.—In addition to the electrocardiographic changes which have been described, we have also observed the development of A-V dissociation, premature systoles of auricular and ventricular origin, nodal rhythm, and ventricular tachycardia. Changes in the electrocardiographic contour which we observed have been described in detail by others.^{2,4,5}

10. *Side Effects of Acetylcholine Administration*.—Acetylcholine was found, in our experiments, to cause marked salivation, with the production of a thick, tenacious sputum which may interfere with respiration. There was stimulation of respiration and speeding of the cardiac rate after the initial slowing. With large doses, transitory convulsions, lasting for less than thirty seconds, may occur. Observations of similar effects have been made in man when large doses of acetylcholine have been used in shock therapy.⁶ Other effects are described elsewhere.^{17,18}

DISCUSSION

It is believed by many that the factors involved in the genesis of auricular fibrillation consist of (a) vagal hyperactivity and (b) a factor described by Nahum and Hoff as the "E" factor or excitatory factor.¹² These observers have included under the "E" factor such influences as thyroxin, electric shock, auricular distention, and mechanical stimulation of the auricles. Smith and Wilson¹⁰ demonstrated that perfusion of the coronary arteries of the heart-lung preparation with anoxemic blood and Mecholyl often resulted in the occurrence of spontaneous auricular fibrillation even in the absence of auricular distention, and that such auricular fibrillation could be abolished by perfusion with oxygenated blood. They also demonstrated, in dogs, that asphyxia potentiated the action of Mecholyl in causing cardiac arrest and auricular fibrillation. Resnick¹¹ reported that anoxemia predisposed the faradically stimulated auricles to fibrillation even when vagal tone was completely removed, and that this predisposition occurred only early in the anoxemic period. The late effects of anoxemia produced by low oxygen mixtures appeared to inhibit the development of auricular fibrillation. A moderate degree of anoxemia produced a relative decrease in the refractory period of the auricular muscle and slowed conduction, both of which tend to favor the maintenance of auricular fibrillation. In Resnick's experiments performed on the dog's heart in situ, none of the animals developed auricular fibrillation spontaneously with anoxic anoxia, and faradic stimulation was used to initiate the auricular fibrillation.

In animals, vagal stimulation alone rarely leads to auricular fibrillation.¹² However, if the auricles are stimulated faradically during vagal excitation, auricular fibrillation nearly always occurs.¹³ Lewis, Drury, and Bulger,¹⁴ and also Andrus and Carter,¹⁵ observed that vagal stimulation shortens the refractory period of auricular muscle remarkably, and that impulses falling early in the relative refractory phase may initiate auricular fibrillation. Andrus and Carter suggested that this is due to the setting up of re-entrant rhythms in muscle which is excitable but in which the conductivity has not yet returned to normal. It has been shown¹⁴ that conductivity in the wall of the right auricle is practically unaffected by the vagus. When, however, the auricles are responding to stimuli

at rates above 300 per minute, then transmission of impulses through the auricles is facilitated by vagal stimulation by virtue of the shortening of the refractory period. In the over-all sense, the action of the vagus on the refractory period favors the development and maintenance of auricular fibrillation.

Numerous investigators have been able to produce auricular fibrillation in the dog and in man by using the parasympathomimetic agents, Mecholyl and acetylcholine. Goldenberg and Rothberger⁴ noted that cats and dogs fibrillated far more readily following the administration of acetylcholine than following vagal stimulation. Iglauer, Davis, and Altschule³ reported that Mecholyl given intravenously caused auricular fibrillation in seven of ten dogs tested. Several investigators have reported that the intra-arterial and intravenous injection of acetylcholine resulted in the production of auricular fibrillation, in isolated cases, in man. Of seventeen patients who received 40 mg. of acetylcholine injected into the common carotid artery, three developed transient auricular fibrillation.⁷ Observations on thirteen patients who received 80 mg. of acetylcholine intravenously indicated the production of auricular fibrillation in one case only. Four additional patients received acetylcholine intravenously in doses of from 100 to 700 mg., with auricular fibrillation resulting in one patient.⁶ No information regarding the hemoglobin levels in these subjects was given. Thus, it is clear that vagus-like substances alone may occasionally cause the development of auricular fibrillation in man and, more frequently, in dogs. In susceptible dogs we were able by continued infusion of acetylcholine to maintain auricular fibrillation for long periods. While the importance of vagal stimulation and anoxic anoxia upon the production of auricular fibrillation is apparent from the foregoing evidence, there are, so far as we know, no published data regarding the influence of anemia upon this arrhythmia. In this laboratory, Schlichter and associates,¹⁹ using acetylcholine intravenously in the determination of circulation time in human subjects, have recently observed the production of auricular fibrillation in an occasional patient. In a subsequent analysis, Schlichter¹ found this was prone to occur in patients who were markedly anemic. Furthermore, following transfusion with whole blood, and with no other treatment, the auricular fibrillation was converted to sinus rhythm. This was taken to indicate that anemia may play a role in the genesis and maintenance of auricular fibrillation.

In our experiments, anemia, produced by each of the three different methods employed, resulted in an increased sensitivity of the heart toward the production of A-V block and auricular fibrillation by means of acetylcholine. Since it has already been shown that heightened vagal tone predisposes to auricular fibrillation, it may be reasoned that one of the ways in which anemia acts to favor the development of auricular fibrillation is through this mechanism.

We have, however, eliminated the vagal factor in testing the tendency to fibrillate by using a method of biological standardization in which we applied the same amount of vagal stimulation in the pre-anemic and anemic states. Under these conditions an increased tendency to fibrillate during anemia is still manifest, and must be due to other factors, including probably anoxia of the heart. We recognize that our method of assay depends upon the reaction of the A-V node, and we cannot state with certainty that a parallel degree of sensitivity occurs in the auricular muscle.

Acetylphenylhydrazine and *n*-propyl disulfide are two agents of distinctly different chemical composition, both of which produce a hemolytic type of anemia. It would appear that the common factor involved in the increased sensitivity in all procedures was associated with the anemia itself and was not a specific action of either the acetylphenylhydrazine or the *n*-propyl disulfide. We call attention to the increase in sensitivity which occurs shortly after the administration of either of these substances and which precedes any marked fall in the hemoglobin level. It is clear, however, that maximum sensitivity does not become manifest until the low point of the anemia is reached. And this point is not reached until several days have elapsed following the last dose of the drug. The explanation for the early development of sensitivity is not clear, nor is the explanation for the difference in sensitivities observed after acetylphenylhydrazine as compared with *n*-propyl disulfide. The explanation for both these factors may depend on the exact mechanism by which these hemolytic agents attack red blood cells. For hemorrhagic anemia a different mechanism must be invoked. It is probable, however, that anemia, per se, plays the major role in the mechanism of the sensitivity phenomena, and acts by decreasing the amount of oxygen available to the myocardium. Ventricular standstill resulting from A-V block and the increased work of the heart in anemia both contribute toward anoxia of the myocardium. We cannot, however, rule out the possibility that the sensitivity phenomena may be the reflection of a reduced esterase content of the blood. The factor of increasing rapidity of the circulation in anemia would seem to have been ruled out. It is known that the circulation time of the dog determined by the acetylcholine method varies from four to nine seconds, and is quite inconstant even in the same dog at rest. Measurements of the heart rates and circulation times from our own records lead us to consider that the increase in rate and the decreased circulation time are not sufficient in themselves to account for the increased sensitivity seen. Furthermore, on a number of occasions blood was aspirated into a syringe containing the minimal standardizing dose and a good admixture produced. Injection was delayed three to five seconds and was followed by A-V block. This indicates a relatively slow rate of hydrolysis of acetylcholine in the dog.

Sabine¹⁶ has pointed out that the dog normally has a higher esterase activity in the plasma than in whole blood. This is the opposite of the situation found in man. When hemorrhagic anemia was produced in the dog, and the hematocrit fell, a fall of the plasma esterase occurred, but the whole blood esterase fell only slightly. This was due to a marked increase in the esterase content of the red cells. Similar studies in anemic states in man indicated that there was a marked rise in the esterase content of the cells which could not be wholly correlated with the rise in reticulocytes and young cells in the circulating blood. It is probable, therefore, that in anemia produced in dogs by the method described, the whole blood esterase falls little or not at all. However, since we do not know whether in the dog the plasma esterase or the cell esterase is of prime importance in hydrolyzing injected acetylcholine, it is impossible to rule out entirely a fall in plasma esterase as a contributing factor in the increased sensitivity to acetylcholine seen in anemia. Blood pH changes may also play a role here.

Our results are parallel to those of Smith and Wilson,¹⁰ who demonstrated that asphyxia sensitizes the heart to Mecholyl, and to those of others^{8,9} who showed that anoxemia enhances vagal cardiac action. Our results support the concept that anemia may play a role in the genesis of supraventricular conduction disturbances, including auricular fibrillation.

Finally, tracings obtained during our experiments offer no support for the concept that auricular fibrillation arises either from the operation of a parasystolic focus, or as the result of multiple, rapidly beating, ectopic pacemakers in competition with each other. The evidence fosters instead the belief that auricular fibrillation originates from a single initial impulse which undergoes re-entry within the auricles and gives rise to multiple continuous re-entries from several points.

SUMMARY

1. The minimal dose of acetylcholine required to produce second degree A-V block (the minimal standardizing dose) was determined in thirty-one dogs. Although the minimal standardizing dose varies widely from animal to animal, it remains relatively constant for the same animal over long periods of time. The minimal standardizing dose bears a crude relationship to the hemoglobin level. Doses ten times and twenty times the minimal standardizing dose were also given. With such doses auricular fibrillation occurred in approximately 50 per cent of the animals tested.

2. Anemia was produced by phenylhydrazine, *n*-propyl disulfide, and hemorrhage. An increased sensitivity toward the development of A-V block and auricular fibrillation which roughly paralleled the course of the anemia was observed. Fifty per cent of the dogs which did not fibrillate with control injections of acetylcholine fibrillated following the onset of the anemia. Animals which fibrillated with control injections fibrillated during anemia with smaller doses of acetylcholine.

3. It is suggested that the increased sensitivity of the heart to acetylcholine in anemia is due to anoxia of the myocardium. Decreased concentration of effectiveness of cholinesterase may also play a role.

4. In dogs in which acetylcholine causes auricular fibrillation, there is a semidirect relationship between the dosage of acetylcholine given and the length of time during which the auricles fibrillate. There is also a relationship between the magnitude of the dose and the length of time during which the A-V block persists.

5. The development of auricular fibrillation was preceded in almost every instance by the occurrence of intra-auricular block and A-V block. It is suggested on the basis of the contour of our records and in support of previous reports from this department that auricular re-entry is the mechanism of the genesis of auricular fibrillation.

6. Electrocardiographic changes seen after the administration of acetylcholine included changes in the contour of the P waves and the T waves and shifts in the P-Q and S-T segments. Arrhythmias seen included auricular fibrillation and flutter, ventricular tachycardia, auricular and ventricular premature systoles, nodal rhythm, and A-V dissociation.

We are indebted to Dr. L. N. Katz for his suggestions and advice in the conduct of these studies and in the preparation of this report.

REFERENCES

1. Schlichter, J. G.: Etiology of Auricular Fibrillation and the Mechanism of its Perpetuation. *AM. HEART J.* 37:674, 1949.
2. Noth, P. H., Essex, H. E., and Barnes, A. R.: The Effect of the Intravenous Injection of Acetylcholine on the Electrocardiogram of the Dog, *Proc. Staff Meet. Mayo Clin.* 14:348, 1939.
3. Iglauer, A., Davis, D., and Altschule, M. D.: Auricular Fibrillation in Normal Intact Animals After the Intravenous Injection of Mecholyl, *AM. HEART J.* 22:47, 1941.
4. Goldenberg, M., and Rothberger, C. J.: Ueber die Wirkung von Acetylcholin auf das Warmblutherz, *Ztschr. f. d. ges. exper. Med.* 94:151, 1934.
5. Wilburne, M., Schlichter, J. G., and Simon, A. J.: The Effect of Acetylcholine on the Heart. An Electrocardiographic Study in the Heart, *Arch. internat. de pharmacodyn. et de therap.* 76:63, 1948.
6. Stigaard, A.: Electrocardiographic Observations During Intravenous Injections of Acetylcholine, *Acta med. Scandinav.* 118:313, 1944.
7. Battro, A., and Lanari, A.: Injection intra-carotidienne d'acetylcholine chez l'homme, *Compt. rend. Soc. de biol.* 125:541, 1937.
8. Heymans, C., Bouckaert, J. J., and Samaan, A.: Influences des variations de la teneur du sang en oxygene et en CO₂ sur l'excitabilité reflexe et directe des elements centroux et peripheriques des nerfs cardio-regulatur, *Arch. internat. de pharmacodyn. et de therap.* 48:457, 1934.
9. Richard, A.: Action de l'asphyxie sur la cardio-inhibition vagale, *Ann. Rev. Physiol.* 12:774, 1936.
10. Smith, J. M., and Wilson, K. S.: Studies on the Production and Maintenance of Experimental Auricular Fibrillation, *AM. HEART J.* 27:176, 1944.
11. Resnick, W. H.: Observations on the Effect of Anoxemia on the Heart. III. Changes in the Auricles With Particular Reference to the Relationship Between Anoxemia and Auricular Fibrillation, *Federation Proc.* 6:123, 1947.
12. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl- β -Methylcholine With Observations on the Role of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* 105:254, 1935.
13. Lewis, T., Drury, A. N., and Iliescu, C. C.: Further Observations Upon the State of Rapid Re-excitation of the Auricles, *Heart* 8:311, 1921.
14. Lewis, T., Drury, A. N., and Bulger, H. S.: Observations Upon Flutter and Fibrillation. Part VI. The Refractory Period and Rate of Propagation in the Auricle: Their Relation to Block in the Auricular Walls and to Flutter, *Heart* 8:83, 1921.
15. Andrus, E. C., and Carter, E. P.: The Refractory Period of the Normally Beating Dog's Auricle, *J. Exper. Med.* 51:357, 1930.
16. Sabine, J. C.: Choline Esterase of Blood Cells and Plasma in Blood Dyscrasias With Special Reference to Pernicious Anemia, *J. Clin. Investigation* 19:833, 1940.
17. Carmichael, E. A., and Fraser, R. F.: The Effects of Acetylcholine in Man, *Heart* 16:263, 1933.
18. Ellis, L. B., and Weiss, S.: A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-arterial Injection of Acetylcholine, *J. Pharmacol. & Exper. Therap.* 44:235, 1932.
19. Schlichter, J. G., Wilburne, M., and Grossman, M.: The Use of Acetylcholine in the Objective Determination of Circulation Time in Man, *Am. J. M. Sc.*, 216:523, 1948.

THE INFLUENCE OF VAGAL ACTIVITY ON HEART BLOCK

A STUDY OF THE EFFECT OF OXYGEN, MECHOLYL, AND ATROPINE ON AURICULOVENTRICULAR CONDUCTION TIME

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THE reports of Bruenn,¹ Keith,² and Robinson³ have shown clearly that large doses of atropine will shorten the P-R interval in a majority of the cases of partial heart block associated with acute rheumatic fever, as well as in certain vagotonic individuals. The findings of Logue and Hanson^{4,5} indicated that this effect is not specific for acute rheumatic fever. The last named authors studied thirty-eight individuals with prolonged P-R intervals associated with various diagnoses and found that twenty-five (65 per cent) showed a return of the P-R interval to normal after administration of 0.96 mg. of atropine sulfate intravenously. There was no correlation between the clinical diagnosis and the effectiveness of atropine; however, it is of interest that in this group seven patients with rheumatic fever showed a return of the P-R interval to normal while six did not.

The reduction of the P-R interval in a control group was found by Bruenn¹ and Keith² to be less than that in rheumatic subjects with prolonged P-R intervals. This is due very probably to the fact that in normal individuals the P-R interval is closer to the minimum possible conduction time; hence, less shortening is possible. Bruenn¹ has interpreted these results to indicate that an increased vagal tone exists in acute rheumatic fever and has suggested that the site of the lesion may be in the central nervous system, probably in the medulla. Robinson³ concurred in the opinion that an increased vagal tone exists in acute rheumatic fever with partial heart block. However, Logue and Hanson⁴ felt that the effect of atropine did not preclude a pathologic change either in the heart muscle or in the conduction system and that the change in vagal tone might be due to altered physiology at the myoneural junction.

Dameshek, Loman, and Myerson⁶ found that the P-R interval increased in almost every instance in normal individuals following the administration of Mecholyl. The maximum effect occurred within two to four minutes and the average percentage increase was 46 per cent. This was abolished within thirty to sixty seconds after the intravenous injection of atropine.

That heart block of all grades, including complete heart block, may be produced by asphyxia and succeeded by recovery, independent of vagus activity, was shown experimentally by Lewis and Mathison.⁷ Persistent heart block of a high grade is generally considered to be due to intrinsic heart disease

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and temporary or transient block to be of vagal origin.^{7,8} When heart block responds to atropine, the question arises as to whether the reduction in conduction time is due to the abolition of an increased primary central neurogenic effect or to a normal neurogenic effect upon a heart rendered more susceptible to vagal influence by some metabolic alteration in the conduction system, at the myoneural junction, or in the myocardium.

The present study was undertaken to investigate the effect of vagal activity on unselected cases of heart block. In addition to the effect of atropine, the effects of breathing 100 per cent oxygen and of the subcutaneous injection of acetyl-beta-methylcholine chloride (Mecholyl) on patients with heart block were studied.

METHOD OF STUDY

The subjects used in this study were fifty-one unselected patients from the wards and outpatient clinics of Duke Hospital whose electrocardiograms revealed a P-R interval of 0.21 second or over manifested in all leads, or higher degrees of heart block. No attempt was made to select the patients with regard to age, general condition, or diagnosis. The distribution of the patients according to age is shown in Table I, and the associated diagnoses are listed in Table II. Mecholyl was not administered to patients with a history of asthma or pulmonary disease.

TABLE I. AGE DISTRIBUTION OF PATIENTS

AGE (YEARS)	PATIENTS RECEIVING ATROPINE ALONE	PATIENTS RECEIVING OXYGEN, ATROPINE, AND MECHOLYL	TOTAL NUMBER OF PATIENTS IN SERIES
0-9	1	0	1
10-19	1	4	5
20-29	3	6	9
30-39	4	2	6
40-49	4	4	8
50-59	5	3	8
60-69	7	3	10
70-79	2	0	2
80-89	2	0	2
Total	29	22	51

TABLE II. CARDIOVASCULAR DIAGNOSES OF PATIENTS COMPOSING GROUPS 1 AND 2

TYPE OF HEART DISEASE	PATIENTS RECEIVING ATROPINE ALONE	PATIENTS RECEIVING OXYGEN, ATROPINE, AND MECHOLYL	TOTAL
None demonstrable	6	5	11
Hypertensive	11	7	18
Arteriosclerotic	6	1	7
Rheumatic, active	2	5	7
Rheumatic, inactive	4	2	6
Congenital	0	1	1
Undiagnosed	0	1	1
Total	29	22	51

The patients were divided into two groups. In Group 1 there were twenty-one patients with partial heart block without dropped beats, four patients with partial heart block and dropped beats, and four patients with complete heart block. In Group 2 there were sixteen patients with partial heart block without dropped beats, four with partial heart block with dropped beats, and two with complete heart block. There were eight patients in each group who were receiving digitalis at the time of this study and of these only one was considered to be definitely intoxicated with the drug. Those patients with partial heart block with dropped beats and those with complete heart block are referred to in Tables IV and V.

In Group 1 a control electrocardiogram was taken and 2.0 to 3.0 mg. of sterile atropine sulfate solution were injected intravenously. (One child, 6 years of age, was given 0.8 milligram.) Electrocardiograms were repeated at various intervals. However, since the maximum effect occurred generally at twenty minutes, records taken at this interval were selected for comparison with the control.

In Group 2 a control electrocardiogram was taken, and the patient was allowed to breathe pure oxygen through a standard Benedict-Roth basal metabolism machine for five minutes. The electrocardiogram was repeated while the patient was still breathing pure oxygen. The oxygen was discontinued, and the needle of a syringe containing 2.0 mg. of sterile atropine sulfate solution was inserted into an arm vein and fixed in place by adhesive tape. The patient then was given a subcutaneous injection of 20 to 25 mg. of Mecholyl, and the electrocardiogram was repeated after an interval of three minutes. As soon as the electrocardiogram was completed, the atropine solution was injected and the final record was taken twenty minutes later.

When the P-R interval varied in any single record, the variation is shown in the table, and the mean is used for comparative purposes. The control record was used for comparison with those records taken after administration of the various drugs. Although it is realized that a P-R interval of 0.21 or even 0.22 second may be normal for some individuals, we have included these instances in this study under the diagnosis of no demonstrable heart disease when such delay was the only manifest abnormality present.

RESULTS

The results in the patients of Group 1 who showed partial heart block without dropped beats are summarized in Table III. Following the injection of atropine, the mean shortening of the P-R interval was 0.044 second, with a range 0.00 to 0.11 second. The mean increase in the cardiac rate was 28.1 beats per minute, with a range of -4 to +82 beats per minute. There was no strict correlation between the increase in rate and the shortening of the P-R interval. In one of the patients in this group blocked premature auricular beats appeared as the auricular rate increased. Among these patients with partial heart block without dropped beats, 52.4 per cent showed a return of the P-R interval to normal; 38.1 per cent showed a reduction of the P-R interval; and 9.5 per cent showed no change.

TABLE III. THE EFFECT OF ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITHOUT DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE OR ASSOCIATED DIAGNOSIS	P-R INTERVAL BEFORE ATROPINE (SEC.)	VENTRICULAR RATE BEFORE ATROPINE	P-R INTERVAL AFTER ATROPINE (SEC.)	VENTRICULAR RATE AFTER ATROPINE	SHORTENING OF P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	DIGITALIS
1	Rheumatic, inactive	0.28	63	0.20	145	0.08	+82	No
2	Rheumatic, inactive	0.28	70	0.28	95	0.00	+25	Yes
3	Rheumatic, inactive	0.28	80	0.24	92	0.04	+12	No
4	Arteriosclerotic	0.24	42	0.20	80	0.04	+38	No
5	Hypertensive	0.22	83	0.20	103	0.02	+21	No
6	Dystrophia myotonica	0.23	68	0.21	79	0.02	+11	No
7	Dystrophia myotonica	0.23	62	0.23	58	0.00	- 4	No
8	Rheumatic, active	0.24	76	0.22	93	0.02	+17	No
9	Hypertensive and cystic lung disease	0.24	64	0.18	78	0.06	+14	Yes
10	Hypertensive	0.32	62	0.24	84	0.08	+22	No
11	None demonstrable	0.24	62	0.22	138	0.02	+76	No
12	Hypertensive	0.24	78	0.20	102	0.04	+24	No
13	Hypertensive	0.28	75	0.22	100	0.06	+25	Yes
14	Peptic ulcer	0.22	72	0.18	90	0.04	+18	No
15	Arthritis	0.26	58	0.20	58	0.06	0	No
16	Arteriosclerotic	0.23	63	0.18	72	0.05	+ 9	No
17	Arteriosclerotic	0.24	70	0.16	80	0.08	+10	Yes
18	Hypertensive	0.27	74	0.24	72	0.03	- 2	Yes
19	Bronchiectasis	0.26-0.28	74	0.16	111	0.11	+37	No
20	Rheumatic, active	0.20-0.21	67	0.19	115	0.015	+48	No
21	Arteriosclerotic	0.28	72	0.14-0.28	90* 72	0.07	+18	Yes

*After atropine, dropped beats appeared after premature auricular beats. Auricular rate 90, ventricular rate 72.

The effects of atropine on four patients not included in the figures just cited are summarized in Table IV. Two of these four had partial heart block with dropped beats; after atropine, one patient with a 2:1 A-V ratio showed an increase in the cardiac rate without a change in the P-R interval and the other showed a decrease in the P-R interval and the number of dropped beats. In one patient with frequent areas of sinoauricular block and nodal escape, as well as partial heart block, the sinoauricular block was abolished by atropine without an effect on the P-R interval. In one patient with partial heart block and a shifting pacemaker, nodal rhythm was produced by atropine.

Atropine had no effect on the A-V conduction time in four cases of complete heart block in this group. The effect on the auricular and ventricular rates is shown in Table V.

The results in the patients comprising Group 2 who exhibited partial heart block without dropped beats are summarized in Table VI. The average change in the cardiac rate after oxygen was breathed for five minutes was less than one beat per minute, and there was no change in the P-R interval. Therefore, these results are omitted from the table.

The mean change in the P-R interval after the injection of 20 to 25 mg. of Mecholyl subcutaneously was a decrease of 0.032 second with a range of +0.03 second to -0.14 second. The mean increase in the auricular rate was 25.7 beats per minute with a range of -1 to +50 beats per minute, and the mean increase in the ventricular rate was 20.3 beats per minute with a range of -42 to +50 beats per minute. In two patients with active rheumatic fever, A-V dissociation was produced in one and a 2:1 heart block in the other. The P-R interval was slightly increased in a third patient with no demonstrable heart disease. In this group the P-R interval returned to normal after Mecholyl in 37.5 per cent of the patients; decreased, but not to normal, in 31.3 per cent; increased in 25.0 per cent; and was unchanged in 6.2 per cent.

The mean change in the P-R interval in the patients comprising Group 2 after the injection of 2.0 mg. of atropine sulfate, which was given intravenously shortly after Mecholyl had been administered, was a decrease of 0.061 second with a range of 0.00 to -0.13 second. The mean increase in cardiac rate was 25.3 beats per minute with a range of -2 to +52 beats per minute. In two patients in whom A-V dissociation and 2:1 block had occurred following the injection of Mecholyl, 1:1 rhythm was restored after atropine, and the P-R interval either returned to the previous control level or was shortened. Following the injection of atropine, the P-R interval returned to normal in 62.5 per cent of the patients; decreased, but not to normal, in 25 per cent; and was unchanged in 12.5 per cent.

Four patients with partial heart block and dropped beats were given oxygen, Mecholyl, and atropine, in that order. The results are given in Table VII. In no instance did Mecholyl abolish dropped beats. However, in two patients the dropped beats were abolished by atropine, and the P-R interval shortened to normal or just beyond normal limits.

TABLE IV. THE EFFECT OF ATROPINE ON HEART RATE AND DURATION OF THE P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITH DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER ATROPINE			CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	CHANGE IN AURICULAR RATE	DIGITALIS
		P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE				
1	Hypertensive	0.19	80	40	0.19	104	52	0.00	+12	+24	No
2	Arteriosclerotic	0.15-0.36	88	55	0.23	78	75	-0.025	+20	-10	No
3	Hypertensive	0.24	*	35	0.24	82	82	0.00	+47		No
4	Arteriosclerotic	0.20†	36	36	(R-P) 0.14	60	60		+24		Yes

*This patient showed sinoauricular block with nodal escape. Atropine abolished sinoauricular block.

†Shifting pacemaker changed to nodal rhythm by atropine.

TABLE V. THE EFFECT OF ATROPINE ON AURICULAR AND VENTRICULAR RATES OF PATIENTS WITH COMPLETE HEART BLOCK*

CASE NO.	TYPE OF HEART DISEASE	CONTROL		AFTER ATROPINE		CHANGE IN VENTRICULAR RATE	CHANGE IN AURICULAR RATE	DIGITALIS
		AURICULAR RATE	VENTRICULAR RATE	AURICULAR RATE	VENTRICULAR RATE			
1	Hypertensive	A.F.†	38	A.F.†	38	0	0	Yes
2	Hypertensive	118	42	126	42	0	+8	No
3	Hypertensive	75	45	100	55	+10	+25	No
4	Rheumatic	70	26	90	31	+5	+20	No

*There was no effect on A-V conduction.

†A. F. = auricular fibrillation.

TABLE VI. THE EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVALS IN PATIENTS WITH PARTIAL HEART BLOCK WITHOUT DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE OR ASSOCIATED DIAGNOSIS	CONTROL		AFTER MECHOLYL					AFTER ATROPINE				DIGITALIS
		P-R INTER-VAL (SEC.)	VEN-TRICU-LAR RATE	P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICU-LAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN VEN-TRICU-LAR RATE	P-R INTER-VAL (SEC.)	VEN-TRICU-LAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN VEN-TRICU-LAR RATE	
1	None demonstrable	0.22-0.20	74	0.20-0.19	120	120	-0.015	+50	0.20-0.19	102	-0.015	+28	No
2	Rheumatic, active	0.24	110	0.19*	113	97		-13*	0.24	120	0	+10	Yes
3	Rheumatic, active	0.36	76	0.22	94	94	-0.14	+18	0.24	115	-0.12	+39	Yes
4	None demonstrable	0.24	64	0.26-0.28	92	92	+0.03	+28	0.24	90	0	+26	No
5	Hypertensive	0.23	90	0.22	140	140	-0.01	+50	0.20	142	-0.03	+52	No
6	Rheumatic, active	0.24	100	0.20	112	56	-0.04	+12	0.16	112	-0.08	+12	Yes
7	Arteriosclerotic	0.21-0.24	71	0.20-0.21	70	70	-0.02	-1	0.20	74	-0.025	+ 3	Yes
8	None demonstrable	0.33	66	0.24	112	112	-0.09	+46	0.20-0.22	95	-0.12	+29	No
9	Cardiac enlargement undiagnosed	0.28-0.32	88	0.28-0.32	100	100	0	+12	0.22-0.24	118	-0.07	+30	No
10	Myxedema	0.22	68	0.24	90	90	+0.02	+22	0.18	100	-0.04	+32	No
11	Rheumatic, active	0.28	92	0.24	108	108	-0.04	+16	0.16-0.18	143	-0.11	+51	Yes
12	Rheumatic, active	0.23	112	0.26	140	70	+0.03	-42†	0.22	110	-0.01	- 2	No
13	None demonstrable	0.29	92	0.20	140	140	-0.09	+48	0.19	128	-0.10	+37	No
14	Hypertensive	0.26-0.32	72	0.20	100	100	-0.09	+28	0.16	94	-0.13	+22	No
15	Hypertensive	0.21	60	0.18	86	86	-0.03	+26	0.12	84	-0.09	+24	Yes
16	Rheumatic, inactive with subacute bacterial endocarditis	0.23	110	0.20	136	136	-0.03	+26	0.17-0.19	122	-0.05	+12	No

*A-V dissociation appeared after Mecholyl; following atropine, sinus rhythm was restored.
†2:1 block appeared after Mecholyl; atropine restored sinus rhythm.

TABLE VII. THE EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITH DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER MECHOLYL						AFTER ATROPINE					DIGITALIS	
		P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN AURIC-ULAR RATE	CHANGE IN VEN-TRICULAR RATE	P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN AURIC-ULAR RATE		CHANGE IN VEN-TRICULAR RATE
1	Hypertensive	0.20-0.32	65	44	0.16-0.30	100	60	-0.03	35	15	-0.065	25	90	90	25	46	Yes
2	Hypertensive	0.20-0.24	90	89	0.20-0.24	72	70	-0.02	-18	-19	-0.02	34	62	62	34	-28	No
3	Hypertensive	0.18-0.26	80	40	0.20-0.28	80	78	+0.02	0	38	-0.02	6	86	86	6	46	Yes
4	Hypertensive	0.20	76	38	0.20	62	35	0	-14	-3	0	30	53	53	30	15	No

TABLE VIII. EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH COMPLETE HEART BLOCK

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER MECHOLYL						AFTER ATROPINE					DIGITALIS	
		P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN AURIC-ULAR RATE	CHANGE IN VEN-TRICULAR RATE	P-R INTER-VAL (SEC.)	AURIC-ULAR RATE	VEN-TRICULAR RATE	CHANGE IN P-R INTER-VAL (SEC.)	CHANGE IN AURIC-ULAR RATE		CHANGE IN VEN-TRICULAR RATE
1	Congenital heart block	0.20	68	45	0.20	120	60	0	52	15	0.19	140	70	-0.01	72	25	No
2	Rheumatic, inactive		78	40		78	40		0	0		126	70		48	30	No

Oxygen, Mecholyl, and atropine, administered in that sequence, had no effect on one patient with complete heart block other than an increase in both auricular and ventricular rates after atropine. In a second patient with A-V dissociation, 2:1 block occurred after the administration of oxygen and remained after the administration of both Mecholyl and atropine. These results are shown in Table VIII.

There was no predictable relationship between the reaction to atropine or Mecholyl and the presence or absence of digitalis in either group. One patient in Group 2 who was thought to be intoxicated with digitalis (Case 3, Table VII) showed slight prolongation of the P-R interval with a decrease in the number of dropped beats after Mecholyl, and a 1:1 response with a normal P-R interval after atropine.

The blood pressure was recorded in about one-half of the patients in Group 2, and in general there was a drop after the injection of Mecholyl with an immediate rise after atropine followed by a gradual fall to the previous control level at the end of fifteen minutes.

No serious reactions were observed to follow the administration of any of these drugs under the conditions of these experiments. One patient complained of discomfort because of tachycardia following the injection of atropine and several noted dizziness or slight drowsiness. The majority of the patients who received Mecholyl noted temporary discomfort consisting of sweating, increased salivation, tightness in the chest, and dyspnea. In no case did the chest symptoms suggest coronary insufficiency, and in no case did the electrocardiogram show depression of the RS-T segment consistent with coronary insufficiency. In each instance the unpleasant symptoms from Mecholyl were abolished within sixty seconds by the intravenous injection of atropine. The effects of atropine generally were dissipated at the end of two hours.

DISCUSSION

In this study the mean shortening of the P-R interval after the administration of atropine to unselected patients with partial heart block was found to be of similar magnitude to that reported by Keith² and by Robinson,³ who studied patients with rheumatic fever, but not so great as that reported by Bruenn.¹ Our results in general confirm the findings of Logue and Hanson⁴ that atropine will shorten to normal, or significantly reduce the P-R interval in a majority of unselected cases of partial heart block, regardless of the etiology or the associated disease. An atropine test, therefore, is of little value in differentiating between heart block of neurogenic origin and that due to myocardial disease.

The effects of Mecholyl and atropine, when given in this sequence, upon the cardiac rate and the blood pressure were found to agree in general with those observed by Dameshek, Loman, and Myerson.⁶ Following the administration of Mecholyl, if atropine is given intravenously at the time of the fall in blood pressure, there is a prompt, sharp, and sudden rise in blood pressure above the previous normal level. This suggests that when the action of

Mecholyl is abolished by atropine there is a reflex pressor response from an increase in circulating adrenalin as a result of the initial fall in blood pressure. In favor of this view is the fact that when atropine was given prior to Mecholyl to four normal subjects there was no significant fall in blood pressure initially and no secondary rise in blood pressure. The pressor response, therefore, is probably of the same nature as that occurring during the histamine test for pheochromocytoma suggested by Roth and Kvale⁹ but differs very greatly in magnitude.

We found the change in the P-R interval which followed the injection of Mecholyl to be unpredictable, in contradistinction to the findings of Dameshek, Loman, and Myerson.⁶ These authors, using normal individuals, noted an increase in A-V conduction time in almost every instance, while it was observed by us that in patients with partial heart block without dropped beats, well over one-half showed a decrease, and only one-fourth showed a definite increase in the P-R interval.

Acetylcholine in large dosage has been shown by Hoffmann and associates¹⁰ and by McDowall¹¹ to produce a stimulating effect on the atropinized heart but not on the unatropinized heart in isolated perfusion experiments. While the results of heart-lung experiments cannot be applied directly to human pharmacology, they do suggest the complex nature of the problem. The paradoxical effects of Mecholyl on cardiac rate and A-V conduction time in the human subject indicate that the magnitude of the various side effects of the drug, unrelated to its direct action on the myoneural junction, often may be as great as the vagomimetic effect.

The unpredictable effect of Mecholyl on A-V conduction time in patients with partial heart block suggests that this drug is of no value in evaluating the part played by vagal activity in unselected cases of heart block. It is apparent from our observations that heart block, per se, does not contraindicate the use of Mecholyl.

These results do not preclude the possibility that the action of these drugs on A-V conduction time is related to changes in coronary blood flow. Although we produced no significant change by having the patients breathe pure oxygen, this does not eliminate the possibility that changes in the caliber of the vessels supplying the conducting tissues may be of importance. Wedd,¹² Essex and associates,¹³ and Katz and Lindner¹⁴ have shown that Mecholyl increases the coronary blood flow. The effects of atropine on coronary blood flow are somewhat conflicting. Essex and co-workers¹³ found atropine to increase coronary blood flow, while Katz and Lindner¹⁴ observed a weak vasoconstrictor effect on the coronary arteries. Halsey¹⁵ noted that partial heart block associated with digitalis intoxication in the dog could be reduced significantly by amyl nitrite but believed this to be due to a lessened vagal effect as a result of a drop in blood pressure. It should be pointed out, however, that large doses of digitalis in the dog cause constriction of the coronary vessels. The results of our observations on the response of human subjects to atropine, Mecholyl, and oxygen do not serve to delineate the physiologic mechanisms involved in the production of heart block. These drugs do not determine whether

alterations of conduction time are due to increased central neurogenic effects or to normal neurogenic influences acting upon hearts rendered more susceptible to vagal influence as the result of metabolic changes in the conducting system, in the myoneural junction, or in the myocardium itself.

SUMMARY AND CONCLUSION

Fifty-one cases of heart block associated with various etiological factors were studied electrocardiographically for changes in the P-R interval after the administration of atropine. In twenty-two of these cases the effects of oxygen and Mecholyl were analyzed and the results compared.

Both atropine and Mecholyl were found to decrease the P-R interval in a majority of these cases, but atropine proved the more effective drug. It is concluded that atropine, Mecholyl, and oxygen are of no value in determining either the etiology of heart block or the underlying physiologic mechanisms in human subjects.

REFERENCES

1. Bruenn, H. G.: The Mechanism of Impaired Auriculoventricular Conduction in Acute Rheumatic Fever, *AM. HEART J.* 13:413, 1937.
2. Keith, J.: Over-stimulation of the Vagus Nerve in Rheumatic Fever, *Quart. J. Med.* 7:29, 1938.
3. Robinson, R. W.: Effect of Atropine Upon the Prolongation of the P-R Interval Found in Acute Rheumatic Fever and Certain Vagotonic Persons, *AM. HEART J.* 29:378, 1945.
4. Logue, R. B., and Hanson, J. F.: Heart Block: A Study of 100 Cases With Prolonged P-R Interval, *Am. J. M. Sc.* 207:765, 1944.
5. Logue, R. B., and Hanson, J. F.: Complete Heart Block in German Measles, *AM. HEART J.* 30:205, 1945.
6. Dameshek, W., Loman, J., and Myerson, A.: Human Autonomic Pharmacology. VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmin, Benzedrine—With Especial Reference to the Electrocardiogram, *Am. J. M. Sc.* 195:88, 1938.
7. Lewis, T., and Mathison, G. C.: Auriculo-Ventricular Heart-Block as a Result of Asphyxia, *Heart* 2:47, 1910.
8. Lewis, T., Drury, A. N., and Iliescu, C. C.: Some Observations Upon Atropine and Strophanthin, *Heart* 9:21, 1921.
9. Roth, G. M., and Kvale, W. F.: A Tentative Test for Pheochromocytoma, *Am. J. M. Sc.* 210:653, 1945.
10. Hoffmann, F., Hoffmann, E. J., Middleton, S., and Talesnik, J.: The Stimulating Effect of Acetylcholine on the Mammalian Heart and the Liberation of an Epinephrine-like Substance by the Isolated Heart, *Am. J. Physiol.* 144:189, 1945.
11. McDowall, R. J. S.: The Stimulating Action of Acetylcholine on the Heart, *J. Physiol.* 104:392, 1946.
12. Wedd, A. M.: The Action of Certain Choline Derivatives on the Coronary Flow, *J. Pharmacol. & Exper. Therap.* 57:179, 1936.
13. Essex, H. E., Wégria, R. G. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, *AM. HEART J.* 19:554, 1940.
14. Katz, L. N., and Lindner, E.: The Reaction of the Coronary Vessels to Drugs and Other Substances, *J. A. M. A.* 113:2116, 1939.
15. Halsey, J. T.: The Digitalized Dog's Heart as Affected by Amyl Nitrite or Atropine, Studied Electrocardiographically, *J. Exper. Med.* 25:729, 1917.

RELATIONSHIP OF DICUMAROL ABSORPTION TO GASTRIC FREE HYDROCHLORIC ACID

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THE extreme variability of the prothrombin time response to similar dosages of Dicumarol is a well-established fact. This work was prompted by Dr. Irving Wright of New York City, who raised the question regarding a possible relationship between Dicumarol absorption and gastric acidity. This study, therefore, is concerned chiefly with the relationship of prothrombin response in individuals to the amount of free hydrochloric acid present in the gastric contents after a set dosage of Dicumarol has been given.

METHODS

The subjects studied were all postoperative patients, with the exception of one patient with thrombophlebitis. Most of the patients had had a combined abdominal-perineal resection for carcinoma of the rectum. The average age of the group was 60.5, ranging from 34 to 83 years of age.

The amount of free hydrochloric acid was determined by the histamine fractional test. The figures reported in the study represent the highest degree of free hydrochloric acid found in any one fractional specimen.

The prothrombin time was determined by the same method recommended by Quick¹ with one exception. We used 5.0 c.c. of whole blood to 1.0 c.c. of 1.4 per cent sodium oxalate when we collected the specimens. The results were then recorded as prothrombin concentration, which was determined by the curve shown in Fig. 1. The curve was made with Difco thromboplastin. The diluent used for the blood in making up the curve was saline. Most of the thromboplastin used was Difco. However, some of the early cases were recorded with rabbit-brain thromboplastin freshly made up in our laboratory. The blood for the prothrombin time determinations was drawn at approximately 11 A.M. daily.

A set dosage of Dicumarol was used. Each patient was given 300 mg. at 6 P.M. of the first day. They were then given 150 mg. at 6 P.M. on the second day. Two subjects were not given the 150 mg. on the second day because the prothrombin concentration was so low that this probably would have been dangerous.

In addition to these determinations, each patient had a bromsulfalein retention liver function test and a blood urea calculation.

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DATA

The patients studied were divided into three groups. The first group showed a true achlorhydria. The second group were those having at least one fractional specimen from 1° free hydrochloric acid through 70° free hydrochloric acid. The third group included those with more than 70° free hydrochloric acid.

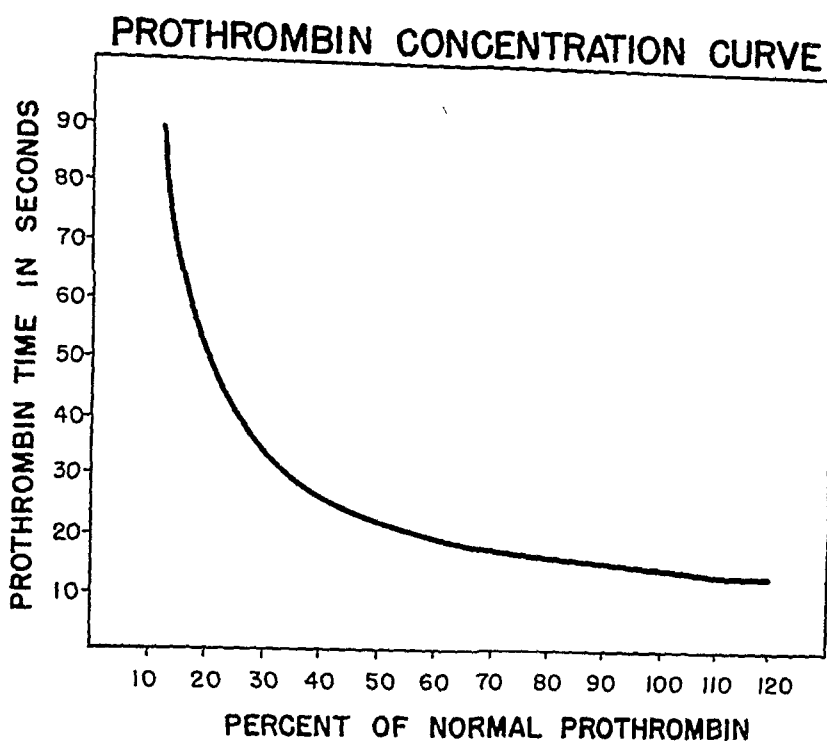


Fig. 1.

The prothrombin concentration average of each group was then calculated for the second, third, and fourth days and compared. The range of prothrombin concentration was also compared in the various groups. The following three tables show the data obtained (Tables I, II, and III).

TABLE I. PROTHROMBIN CONCENTRATION ONE DAY AFTER 300 MILLIGRAMS OF DICUMAROL

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70° + HCL
Number of cases	5	10	17
Average prothrombin concentration (per cent)	66.2	62.4	60.5
Range of prothrombin concentration (per cent)	44-77	32-100	22-100

TABLE II. PROTHROMBIN CONCENTRATION THIRD DAY AFTER GIVING 300 MILLIGRAMS OF DICUMAROL THE FIRST DAY AND 150 MILLIGRAMS THE SECOND DAY

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70° + HCL
Number of cases	5	9	15
Average prothrombin concentration (per cent)	34.6	36.6	39.3
Range of prothrombin concentration (per cent)	30-38	21-54	22-68

TABLE III. PROTHROMBIN CONCENTRATION FOURTH DAY AFTER 300 MILLIGRAMS OF DICUMAROL THE FIRST DAY AND 150 MILLIGRAMS THE SECOND DAY

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70° + FREE HCL
Number of cases	4	8	15
Average prothrombin concentration	29.8	33.3	39.7
Range of prothrombin concentration	26-34	15-86	15-85

Similar data were then computed on two sets of patients. The first set, containing nineteen patients, had a bromsulfalein retention of 10 per cent or less. The second group contained ten patients having a bromsulfalein retention ranging from 16 per cent to 72 per cent, with an average of 32.8 per cent.

RESULTS

The one most consistent finding was that of an extreme degree of variability in the response of prothrombin time to Dicumarol.

There is a slight increase in the average prothrombin concentration going from the achlorhydria to the hyperacidity groups. However, all groups, especially the two groups containing free hydrochloric acid, showed such a marked variability of response to Dicumarol that the slight increase of the average prothrombin concentration would not seem to be significant.

A definite decrease in the range of variability was noted in the achlorhydria group. Likewise, the group showing free hydrochloric acid revealed a wider fluctuation of prothrombin concentration. However, further breakdown of this group did not reveal any direct relationship between the level of free hydrochloric acid and the prothrombin concentration.

It is the opinion of the writers that the data indicate that there is no correlation between increased or decreased absorption of Dicumarol and gastric acidity.

An interesting finding was the comparison of the prothrombin concentration response in relationship to the bromsulfalein retention liver function test. The differences, surprisingly, were not marked. The range of prothrombin concen-

tration varied from a strong response to very little response. On the first day and fourth day there was some evidence of increased prothrombin response in the group with increased bromsulfalein retention; however, on the third day the same group revealed a decreased prothrombin response, again demonstrating the variability.

CONCLUSIONS

1. A comparison has been made of the prothrombin response to Dicumarol with the amount of free hydrochloric acid present in the gastric contents and no relationship was found.
2. The extreme variability of the prothrombin time following Dicumarol administration was again demonstrated.
3. A decreased range of variability was noted in the achlorhydria group. The significance of this is not understood at the present time.

REFERENCE

1. Quick, A. J.: The Nature of Bleeding in Jaundice, J. A. M. A. 110:1658, 1938.

Clinical Reports

DISSECTING ANEURYSM OF AORTA WITH HEMORRHAGIC INFARCTION OF THE SPINAL CORD AND COMPLETE PARAPLEGIA

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IT IS well known that the clinical picture of dissecting aneurysm of the aorta varies widely both as to symptomatology and objective findings. The neurological manifestations are often bizarre, but, if properly interpreted, may lead to a correct ante-mortem diagnosis.²⁹ Instances of paraplegia and paraparesis caused by spinal cord ischemia which results from rupture and thrombosis of the intercostal arteries have occurred, but the entity is rare, and in most of the reported cases, the spinal cord either has not been examined, or has been studied incompletely. In a survey of 698 recorded cases of dissecting aortic aneurysm, we found only three in which the spinal cord was shown to have been the seat of ischemic necrosis and hemorrhagic infarction.

This paper deals with the clinical and necropsy observations on such a case, which exhibited a feature not hitherto observed, namely, a spinal subarachnoid hemorrhage.

CASE REPORT

H. G. L., a 56-year-old Negro man, while addressing a group of fellow ministers on the afternoon of July 17, 1947, was stricken by a sudden sharp, nonradiating upper substernal pain. After a few seconds this pain disappeared, and following a moment's hesitation, he was able to continue speaking. Five minutes later he experienced a second similar pain in the lower substernal region which radiated into the epigastrium and caused him to collapse and fall to the floor. The pain did not radiate to the back, arms, neck, or jaw. He was carried down from the rostrum and in about thirty minutes he lost consciousness and remained so for an hour. He was removed to the emergency ward of a local hospital, where a diagnosis of acute gastroenteritis was made. After administration of sodium luminal he was observed for several hours, and discharged. During this period of time he had recurrent attacks of generalized, burning, abdominal pain, each lasting five to ten minutes, with complete relief between attacks. At first the pain radiated bilaterally to the back, but later radiation was confined to both flanks.

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On the morning of July 18 the episodes of abdominal pain became more severe and more frequent. He became nauseated and vomited a clear fluid. At 9 A.M. he arose from bed and observed that the right foot was partially paralyzed, one hour later the entire right leg was completely paralyzed, and by noon he had complete paraplegia with numbness from the waist down. At 8 P.M. on July 19, approximately fifty-four hours after the onset of the initial attack of sub-sternal pain, he was admitted to the Cleveland City Hospital with complete motor and sensory paralysis from the waist down. Intermittent abdominal pain radiating to both flanks continued for two days thereafter.

The past history threw no light on his present disability. He had been a minister for seventeen years, was married, and had two healthy children. He had enjoyed good health and had no knowledge of syphilis, tuberculosis, or cardiovascular disease.

Physical examination revealed a well-developed, well-nourished 56-year-old Negro man, complaining of intermittent abdominal pain in spite of heavy sedation with morphine. The temperature was 38° C., the respiratory rate 18, the pulse rate 100, and the blood pressure 150/90 in both arms. The blood pressure did not vary significantly throughout his hospital course. The skin was cool and dry above the umbilicus, warm and moist below. The pupils were equal and reacted well to light and in accommodation. The ocular fundi showed moderate sclerosis of the arteries and the discs were well outlined. The pharynx was diffusely and slightly hyperemic; the trachea was in the midline and no tug was noted. There was moderate nuchal rigidity. The thorax was symmetrical and expansion was bilaterally equal and unrestricted. Percussion and auscultation of the lungs revealed nothing abnormal. The heart was moderately enlarged to the left by percussion. The cardiac mechanism was normal except for numerous premature beats. The heart sounds were not unusual; the aortic second sound was accentuated; and a Grade 2 systolic murmur was heard at the apex. All accessible peripheral arteries were moderately thickened and tortuous. All accessible pulses on the two sides were equal and full. The abdomen was slightly distended but not tender to deep palpation. The liver, kidneys, and spleen were not felt, but the urinary bladder dullness was percussed several finger breadths above the pubic symphysis. Rectal examination revealed poor sphincter tone.

A neurological examination disclosed paralysis of both legs and complete loss of sensation from the level of the eighth dorsal segment down, with a band of hyperesthesia above this level corresponding to the distribution of the seventh dorsal segment. The abdominal and cremasteric, as well as the lower deep tendon reflexes, were totally absent. Ankle and patellar clonus and Babinski's sign were not present. Kernig's sign was absent. The upper reflexes were equal and active.

Laboratory work revealed the urine to be clear amber, acid, with a specific gravity of 1.025 plus 4 albumin, and 1.5 per cent sugar. An occasional white blood cell was present. On subsequent repeated examinations the albumin and sugar disappeared, although occasional white cells were constantly present. The hemogram showed 16 Gm. of hemoglobin, 4,700,000 red blood cells, and 19,600 white cells with a moderate shift to the left. White counts repeated on the sixth and seventh hospital days were 14,000 and 12,200, respectively. The electrocardiogram showed left axis deviation.

Because of the history, course, and findings, a tentative diagnosis was made of dissecting aneurysm of the aorta with paraplegia due to rupture of intercostal arteries and ischemia of the spinal cord. The patient was placed on complete bed rest and given large doses of morphine. These measures, however, failed to control his pain completely. An indwelling catheter was left in the bladder after removal of 1,300 c.c. of urine. The blood Wassermann reaction was negative. The blood urea nitrogen on admission was 50.4 mg. per cent, and dropped to 20.3 mg. per cent four days later. An admission chest film on July 20 showed the heart to be enlarged, the transverse diameter measuring 174 millimeters. A diffuse aneurysmal dilatation of the aorta with slight displacement of the trachea to the right was noted (Fig. 1).

On July 20, his second hospital day, a lumbar puncture was done, the needle being introduced between the fourth and fifth lumbar vertebrae. The spinal fluid pressure was 140 mm. H₂O, which dropped to zero after removal of a few cubic centimeters. Following centrifugation, the supernatant fluid was xanthochromic. A cisternal puncture was done on July 21, and again a grossly bloody spinal fluid was withdrawn, under a pressure of 330 mm. of water. A rise in pres-

sure was demonstrated by jugular compression, but strong abdominal pressure raised the level only 5 millimeters. A lumbar puncture repeated on July 22 revealed the same findings, with a negative Queckenstedt and reversed negative Queckenstedt. The spinal fluid Wassermann reaction was negative.

Because of the subarachnoid hemorrhage and evidence of complete block, the working diagnosis was changed to hematomyelia due either to thrombosis of the anterior spinal artery with hemorrhage, or bleeding from a tumor, possibly a hemangioma. It was felt that the subarachnoid block might be due to a cord tumor, and further diagnostic work was done. A posterior-anterior film of the chest on July 23 showed no change. X-ray films of the spine, including several cone-down views, failed to reveal any abnormality. A neurological consultation was held on July 22, and no change in the objective findings was noted other than an extension of the area of hyperesthesia on the trunk to the level of the fifth dorsal segment. The patient was incontinent of feces

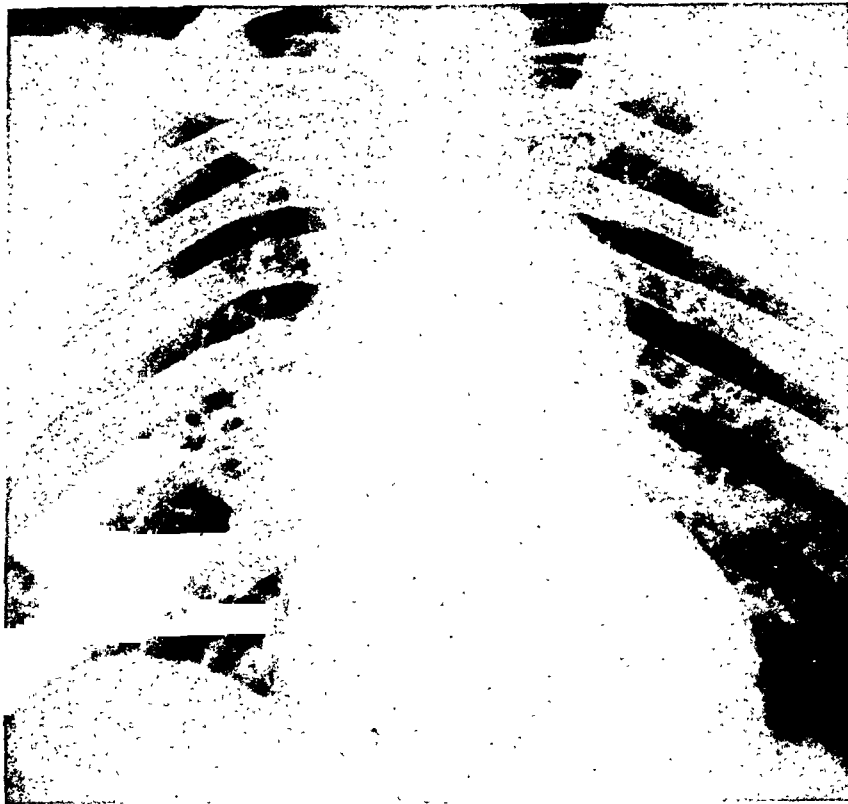


Fig. 1.—X-ray photograph of chest showing aneurysmal dilatation of aorta with trachea displaced to right.

and still required constant urinary drainage. The neurologists confirmed the presence of a complete cord transection producing the picture of spinal shock, and recommended that myelograms be done. The latter were performed on July 25, and were considered nondiagnostic.

On July 24 the patient was seen by a consultant in neurosurgery, who likewise suggested the possibility of a vascular tumor, probably at the level of the seventh dorsal segment, with rupture and subarachnoid hemorrhage. An operation was advised, but immediately following the induction of gas-oxygen-ether anesthesia, the patient expired on the table before an incision could be made. Death occurred on July 26, nine days after the onset of symptoms.

Autopsy.—Anatomical Diagnosis: Dissecting aneurysm of the aorta. Hemorrhagic infarct of spinal cord. Subarachnoid hemorrhage of spinal cord and brain. Arteriolar nephrosclerosis, slight. Cardiac hypertrophy and dilatation (450 grams). Arterial sclerosis (aorta, iliac, cerebral, and visceral, moderate; coronary, slight).

Gross Pathology (Dr. H. Goldman): "The heart is enlarged and weighs 450 grams. Three centimeters above the aortic ring there is a straight clean tear of the intima and part of the media, with finely serrated edges, extending completely around the aorta. The dissection extends proximally to the base of the aortic valve, and distally into the common iliacs just beyond the bifurcation. The dissection of the aortic wall involves nearly its entire circumference throughout its entire length, and extends likewise into the first centimeter of the innominate, left subclavian, left common carotid, right subclavian (which arises anomalously directly from the arch, one centimeter distal to the origin of the left subclavian), coeliac, and superior mesenteric arteries. Re-entry is noted in the left subclavian. The renal arteries are dissected to the hilus but are fully patent. The vertebral arteries are patent and not involved, although the lumen of the left is slightly narrowed at its origin by an arteriosclerotic plaque. All the intercostal and lumbar

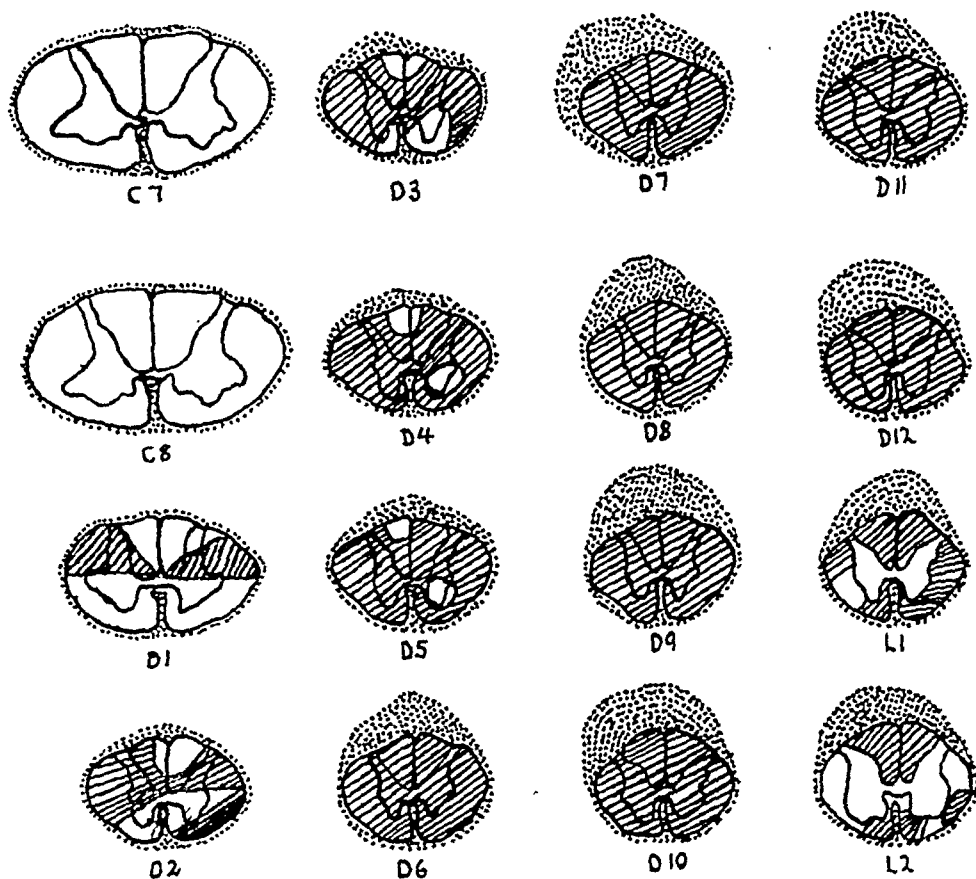


Fig. 2.—Spinal cord involvement from level of C7 to L2. Stripes indicate areas of necrosis, hemorrhage, demyelination, and inflammatory infiltration. Stippled areas represent subarachnoid clot which in some sections showed early organization.

arteries are completely shorn from the aorta, many of them showing thrombus formation. The intimal surface of the aorta is the seat of only moderate arteriosclerosis, proximal to the superior mesenteric artery.

"The pericardial sac is tense and contains 75 c.c. of thin bloody fluid. The pericardial surface is granular and contains adherent fibrin tags. Between the aorta and pulmonary conus in the pericardial reflection there is a friable clot, but an area of rupture into the pericardial space cannot be demonstrated.

"The brain is grossly normal, but there is a layer of blood in the subarachnoid space, involving predominantly the posterior aspect of the cerebral hemispheres, the cerebellum, and the base of the brain posteriorly.

"The cord is removed in toto. On opening the dura, a subarachnoid hemorrhage with clot formation is present over its entire length and circumference. This is most marked from the first thoracic to the first lumbar segments, and reaches its maximum from the seventh dorsal to the twelfth dorsal segments. The cord is soft and diffusely swollen, this being most marked in the same regions where the clot is most extensive. Examination after fixation reveals adherent clot most prominent on the dorsal surface, as described, with a maximum thickness of 3.0 mm. Cut sections of the cord were examined from the level of the seventh cervical to the second lumbar segments, and nowhere can the usual divisions of the cord into white and gray matter be seen."

Microscopic Pathology (Dr. W. Morningstar): "Sections of the aorta in the region of the tear show diffuse cystic necrosis of the media. There is no intimal change in the immediate neighborhood of the tear. Serial sections of the spinal cord from the seventh cervical to the second lumbar segments are examined following staining with hematoxylin and eosin and Weigert's myelin stain. The seventh and eighth cervical segments are uninvolved. The first dorsal segment shows predominantly demyelination and myelomalacia with minimal hemorrhage just posterior to the central canal. This increases in extent until the level of the sixth dorsal segment, where the involvement is complete, resulting in diffuse hemorrhage and necrosis. At the twelfth dorsal segment the change is one of complete necrosis and marked hemorrhage. The first lumbar segment shows necrosis and patchy hemorrhage with the gray matter essentially spared, and the second lumbar segment shows degeneration confined mainly to the posterior columns with an acute inflammatory infiltration of polymorphonuclear leucocytes. For a diagrammatic representation of the changes found at various levels of the spinal cord see Fig. 2.

"The subarachnoid clot shows early organization from the fifth dorsal to the second lumbar segment. Although in one area a small break is demonstrated in the anterior spinal artery, we cannot be certain that this affords adequate explanation of the subarachnoid hemorrhage. No source is found in the brain, and it is felt that the subarachnoid hemorrhage present here is due to extension from below upwards."

DISCUSSION

Neurological complications of dissecting aneurysm of the aorta are by no means uncommon. The actual incidence, however, is difficult to determine, and varies in different series. The reasons for this would appear to be several. As many as 35 per cent of such patients die within the first hour before they have been seen by a physician or before they develop localizing signs.²¹ In addition, the nature of the illness is such as to turn the examiner's attention away from the neurological manifestations unless they are quite apparent. Finally, it becomes obvious in reviewing the literature that complete clinical and pathological descriptions are often lacking, usually because of the author's interest in one particular phase of the disease. Thus, in reviewing 698 recorded cases, we found only 424 that were in any way suitable for analysis. Definite neurological complications were found in eighty-nine cases, or 21 per cent, as compared with 11 per cent in Shennan's²³ series, 18 per cent in the series of Baer and Goldburgh,¹ and 29 per cent in the cases collected by Weisman and Adams²⁹ (Table I). Following the scheme proposed by the last-named authors, forty-one patients with neurological manifestations had ischemic neuropathy, twenty-six had ischemia of the brain, and twenty-two had ischemia of the spinal cord. In some instances, more than one of these features was combined. If doubtful cases were included, which we discarded because of insufficient authenticity or incomplete clinico-pathological correlation, our percentage would approximate the incidence reported by Weisman and Adams.²⁹

TABLE I. INCIDENCE OF NEUROLOGICAL MANIFESTATIONS IN COLLECTED CASES OF DISSECTING ANEURYSM

AUTHOR	CASES ANALYZED	NEUROLOGICAL COMPLICATIONS	
		NO.	%
Shennan ²³	316	45	11
Weisman and Adams ²⁹	38	11	29
Baer and Goldburgh ¹	44	8	18
Present Series	424	83	21

We found a total of twenty-eight well-authenticated instances of paraplegia and paraparesis, an incidence of 6.6 per cent (Table II). Of these, ten represented ischemia of the spinal cord, eleven ischemic neuropathy, three a combination of these two factors, and four could not be determined (Table III). The disparity between the number of patients showing signs of spinal cord ischemia and those resulting in paraplegia lies in the fact that there is probably some gross quantitative relationship between the number of intercostal and lumbar segmental arteries interrupted and the degree of disability resulting. While it is true that disruption of all or most of these vessels results in paralysis, this does not always obtain, since instances have been reported in which no cord signs were noted in spite of marked loss of blood supply as shown later by autopsy.^{9,12,37} The cause of radiation of pain to the lower legs has been a subject of some dispute, being attributed by some to stimulation of nerve endings along the course of dissected vessels,^{17,31} and by others to the initial transient spinal cord ischemia as the dissection extends downward.^{9,26} Reichert and associates¹⁸ have called attention to claudication of the thighs resulting from arteriosclerosis of the lumbar segmental arteries, which, along with cramping of the calves, is a not uncommon occurrence with intercostal artery separation of extensive degree.

Coleman,⁶ in 1898, reported the first case of paraplegia due to spinal cord ischemia, but in only three instances has there been unequivocal evidence, demonstrated by pathological study, of injury to the cord consisting of ischemic necrosis and hemorrhagic infarction: those of Kalischer (1914), Reitter (1916), and Weisman and Adams (1944). Rogers,²¹ in 1939, and Tuohy and his co-workers,²⁶ in 1941, for the first time in the American literature, called specific attention to spinal cord ischemia, but unfortunately little mention was made of post-mortem findings in the spinal cord.

The differential diagnosis of localized spinal cord lesions resulting in bilateral manifestations has been discussed in previous papers, and quite thoroughly in regard to dissecting aneurysm by Weisman and Adams,²⁹ but the presence of a bloody spinal fluid and subarachnoid block in our case deserves some comment. This is of interest, since a clear spinal fluid on puncture has been considered a differential diagnostic criterion favoring the diagnosis of dissecting aneurysm.²¹ Except for a bloody spinal fluid, our case is quite similar to those of Weisman and Adams²⁹ and of Reitter.¹⁹ The latter commented at length on the absence of subarachnoid hemorrhage in his case, and suggested that the spinal fluid pressure

TABLE II. TWENTY-EIGHT CASES OF PARAPLEGIA AND PARAPARESIS RESULTING FROM DISSECTING AORTIC ANEURYSM (698 CASES WERE REVIEWED AND 424 WERE ANALYZED)

AUTHOR	YEAR	TYPE OF INVOLVEMENT	PATHOLOGICAL ANATOMY
Swaine and Latham ²⁴	1855-6	Paraplegia, transient	Common iliac obstruction
Sainet ²²	1857	Paraplegia, permanent	Unknown
Lebert ⁵	1857	Paraplegia, permanent	Unknown
Dickenson ⁷	1862	Paraplegia, permanent	Combined: obstruction of aorta by intimal bulge beyond origin of left subclavian artery
Gordon ¹¹	1863-4	Paraplegia, permanent	Common iliac obstruction
Barth ³	1871	Paraplegia, permanent	Unknown
Coleman ⁶	1898	Paraplegia, transient	Spinal cord ischemia
Ka'ischer ¹³	1914	Paraplegia, permanent	Infarction of spinal cord
Reitter ¹⁹	1916	Paraplegia, permanent	Infarction of spinal cord
Bard and Gardere ²	1925	Paraplegia, permanent	Probable compression of lumen of aorta by intimal bulge
Tyson ²⁷	1931	Paraplegia, permanent	Spinal cord ischemia
Lawrence ¹⁴	1935	Paraplegia, permanent	Compression of iliac lumens by dissection
Glendy, Castleman and White ¹⁰	1937	Paraparesis, permanent	Lower aortic thrombosis
Rogers ²¹	1939	Paraplegia, permanent, right, transient, left	Combined: spinal cord ischemia and iliac obstruction
Cabot Case No. 25382 ⁴	1939	Paraplegia, permanent	Common iliac obstruction by intimal bulge
East ⁸	1939	Paraplegias, transient (two episodes 3.5 years apart)	Common iliac obstruction
Lowell ¹⁶	1940	Paraplegia, duration unknown	Unknown
Tuohy and associates ²⁶	1941	Paraplegia, permanent	Common iliac obstruction by intimal bulge
Tuohy and associates ²⁶	1941	Paraplegia, transient	Combined: obstruction of right iliac and spinal cord ischemia
Weisman and Adams ²⁹	1944	Paraplegia, permanent	Infarction of spinal cord
Weisman and Adams ²⁹	1944	Paraplegia, permanent	Common iliac obstruction
Weisman and Adams ²⁹	1944	Paraparesis, permanent	Common iliac obstruction
Weisman and Adams ²⁹	1944	Paraparesis, permanent	Aortic thrombosis
Ritvo and Votta ²⁰	1944	Paraplegia, permanent	Probable spinal cord ischemia
Thomas ²⁵	1945	Paraplegia (two episodes seven days apart, the second permanent)	Probable spinal cord ischemia
Cabot Case No. 33091 ⁵	1947	Paraplegia, transient	Spinal cord ischemia
Baer and Goldburgh ¹	1948	Paraplegia, transient	Spinal cord ischemia
Warren and McQuown ²⁸	1948	Paraplegia, permanent	Spinal cord ischemia

TABLE III. CAUSE OF PARALYSIS IN TWENTY-EIGHT CASES OF PARAPLEGIA AND PARAPARESIS DUE TO DISSECTING ANEURYSM COLLECTED FROM THE LITERATURE

PATHOLOGICAL BASIS	NO.	%
Ischemia of spinal cord	10	35.5
Ischemic neuropathy	11	39.5
Combined lesions	3	11.0
Undetermined	4	14.0

may have been greater than the intravascular cord pressure, thus preventing the escape of blood into the spinal fluid. In our case just the reverse picture occurred. One of the microscopic sections through the dorsal portion of the cord showed a break in the wall of the anterior spinal artery, but there was no sign of organization of the intraluminal clot, and we cannot be certain but that this finding was factitious.

SUMMARY

A case of dissecting aneurysm of the aorta is presented in which all the intercostal arteries were severed, causing hemorrhagic infarction of the spinal cord and complete motor and sensory paraplegia. To our knowledge it is the first such case reported in which spinal subarachnoid hemorrhage occurred.

REFERENCES

1. Baer, S., and Goldburgh, H. L.: The Varied Clinical Syndromes Produced by Dissecting Aneurysm, *AM. HEART J.* 35:198, 1948.
2. Bard, M. M., and Gardere, H.: Anevrysme dissequant de l'aorte thoraco-abdominale (Presentation de pieces), *Lyon Med.* 135:298, 1925.
3. Barth, O.: *Arch. Heilk.* 12:253, 1871.
4. Cabot Case No. 25382: Dissecting Aneurysm of Aorta With Rupture, *New England J. Med.* 221:471, 1939.
5. Cabot Case No. 33091: Dissecting Aneurysm of Aorta With Rupture Into Left Pleural Space and With Localized Expansion and Partial Healing, *New England J. Med.* 236:327, 1947.
6. Coleman, J. B.: Dissecting Aneurysm, *Lancet* 2:317, 1898.
7. Dickenson, D.: Dissecting Aneurysm of the Aorta, *Tr. Path. Soc. London* 13:48, 1862.
8. East, T.: Dissecting Aneurysm of the Aorta, *Lancet* 2:1017, 1939.
9. Fisher, N. F.: Changes at Orifices of Intercostal Arteries in Dissecting Aneurysm, *Tr. Chicago Path. Soc.* 12:351, 1927.
10. Glendy, R. E., Castleman, B., and White, P. D.: Dissecting Aneurysm of the Aorta, *AM. HEART J.* 13:129, 1937.
11. Gordon, J.: Dissecting Aneurysm of Aorta, *Proc. Path. Soc. Dublin*, 2:84, 1863.
12. Hamburger, M., and Ferris, E. B.: Dissecting Aneurysm: A study of Six Recent Cases, *AM. HEART J.* 16:1, 1938.
13. Kalischer, O.: Aneurysma Dissecans der Aorta mit Paraplegie (Demonstration eines Präparates), *Berliner Klin. Wchnschr.*, 51:2, 1286, 1914.
14. Lawrence, J. H.: The Clinical Symptoms and Signs of Dissecting Aneurysm of the Aorta, *Internat. Clin.* 2:122, 1935.
15. Lebert: *Traite d'anat. pathol.* 1:575, 1857. (Cited by T. Shennan²³).
16. Lowell, W. H.: Dissecting Aortic Aneurysm: Report of Two Cases, *Connecticut M. J.* 4:724, 1940.
17. Mooseberger, W.: Zur Symptomatologie des Aneurysma Dissecans, *Schweiz. med. Wchnschr.* 5:325, 1924.
18. Reichert, F. L., Rytand, D. C., and Bruck, E. L.: Arteriosclerosis of the Lumbar Segmental Arteries Producing Ischemia of the Spinal Cord and Consequent Claudication of the Thighs, *Am. J. M. Sc.* 187:794, 1934.
19. Reitter, K.: Aneurysma Dissecans und Paraplegie, *Zugleich ein Beitrag zur Pathologie der Blutzirkulation in Rückenmark*, *Deutsches Arch. f. klin. Med.* 119:561, 1916.
20. Ritvo, M., and Votta, P. J.: Dissecting Aneurysm: Clinical and Roentgen Manifestations, *Am. J. Roentgenol.* 52:583, 1944.
21. Rogers, H.: Dissecting Aneurysm of the Aorta, *AM. HEART J.* 18:67, 1939.
22. Sainet, M.: Untitled Report. *Bull. Soc. Anat.* 26:25, 1851.
23. Shennan, T.: Dissecting Aneurysm, Medical Research Council, Special Report Series, No. 193, His Majesty's Stationary Office, 1934.
24. Swaine, K., and Latham, P. M.: Case of Dissecting Aneurysm of the Aorta, *Tr. Path. Soc. London*, 7:106, 1855.
25. Thomas, G. T.: A Case of Dissecting Aneurysm of the Aorta Diagnosed During Life, *Clinical J.* 74:20, 1945.
26. Tuohy, E. L., Boman, P. G., and Berdez, G. L.: Spinal Cord Ischemia in Dissecting Aortic Aneurysm, *AM. HEART J.* 22:305, 1941.
27. Tyson, M. D.: Dissecting Aneurysm, *Am. J. Path.* 7:581, 1931.

28. Warren, A. S., and McQuown, A. L.: Dissecting Aneurysm—A Presentation of Ten Cases and a Correlation of Clinical and Pathological Findings, *Am. J. M. Sc.* **215**:209, 1948.
29. Weisman, A. D., and Adams, R. D.: The Neurological Complications of Dissecting Aortic Aneurysm, *Brain* **67**:67, 1944.
30. Whitman, R. G., and Stein, H. B.: A Contribution to the Pathogenesis of Dissecting Mes-aortitis (Babes and Mironescu), Without Dissecting Aneurysm, *J. M. Research* **41**:579, 1924.
31. Wood, E. A.: Dissecting Aneurysm of the Aorta, *Lancet* **I**:402, 1931.
- 32.* Bauersfeld, S. R.: Dissecting Aneurysm of the Aorta: Presentation of Fifteen New Cases and a Review of the Recent Literature, *Ann. Int. Med.* **26**:873, 1947.
- 33.* Cabot Case No. 27292: Dissecting Aneurysm of the Aorta, *New England J. Med.* **225**:116, 1941.
- 34.* Cabot Case No. 28072: Dissecting Aneurysm of Aorta, Old, With Rupture Into Right Iliac Artery, and Fresh, With Rupture Into Pericardium, *New England J. Med.* **226**:273, 1942.
- 35.* Cabot Case No. 28111: Dissecting Aneurysm, With Extension Into Great Vessels of the Neck, Including Complete Transverse Rupture of Outer Cylinder Into Pericardium, *New England J. Med.* **226**:456, 1942.
- 36.* Cabot Case No. 28421: Dissecting Aneurysm of Aorta and Great Vessels of the Neck, *New England J. Med.* **227**:603, 1942.
- 37.* Cabot Case No. 28442: Dissecting Aneurysm of Aorta With Perforation Into Pericardium, *New England J. Med.* **227**:681, 1942.
- 38.* Cabot Case No. 30212: Dissecting Aneurysm of Aorta With Involvement of Major Branches and Occlusion of Right Common Iliac Artery, *New England J. Med.* **230**:651, 1944.
- 39.* Claiborne, T. S.: Dissecting Aneurysm of the Aorta; Report of Case, *J. M. A. Georgia* **28**:12, 1939.
- 40.* Crowell, P. D.: Dissecting Aneurysms of the Aorta; Report of Cases and Review of the Literature, *J. A. M. A.* **77**:2114, 1921.
- 41.* Davis, R. G., and Hall, W. W.: Dissecting Aneurysm; Report of an Unusual Case, *U. S. Naval M. Bull.* **31**:39, 1933.
- 42.* Erdheim, J.: Medionecrosis Aortae Idiopathicae Cistica, *Virchow's Arch. f. path. Anat.* **276**:187, 1930.
- 43.* Farinacci, C. J.: Dissecting Aneurysm of the Aorta; a Report of Five Autopsied Cases, *Bull. School Med. Univ. Maryland* **19**:47, 1934.
- 44.* Flaxman, N.: Dissecting Aneurysm of the Aorta, *AM. HEART J.* **24**:654, 1942.
- 45.* Gager, L. T.: The Symptoms of Dissecting Aneurysm of the Aorta, *Ann. Int. Med.* **2**:658, 1929.
- 46.* Gouley, B. A., and Anderson, E.: Chronic Dissecting Aneurysm of the Aorta Simulating Cardiovascular Disease; Notes on the Associated Aortic Murmurs, *Ann. Int. Med.* **14**:978, 1940.
- 47.* Hargrove, M. D.: Dissecting Aneurysms, *New Orleans M. & S. J.* **91**:678, 1939.
- 48.* Keefer, C. S., and Resnik, W. H.: Dissecting Aneurysm With Signs of Aortic Insufficiency; Report of a Case in Which the Aortic Valves Were Normal, *J. A. M. A.* **85**:422, 1925.
- 49.* Kellog, F., and Heald, A. H.: Dissecting Aneurysm of the Aorta. Report of a Case Diagnosed During Life, *J. A. M. A.* **100**:1157, 1932.
- 50.* Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, *Am. J. M. Sc.* **184**:455, 1932.
- 51.* Leitsch, W. H.: Dissecting Aneurysm; With Case Reports, *Bull. School Med. Univ. Maryland* **29**:7, 1944.
- 52.* Logue, R. B.: Dissecting Aneurysm of the Aorta, *Am. J. M. Sc.*, **206**:54, 1943.
- 53.* McCallum, W. G.: Dissecting Aneurysm, *Bull. Johns Hopkins Hosp.* **20**:9, 1909.
- 54.* McGeachy, T. E., and Paullin, J. E.: Dissecting Aneurysm of the Aorta, *J. A. M. A.* **108**:1690, 1937.
- 55.* McLaurin, J. W.: Dissecting Aneurysm in Boy, *New Orleans M. & S. J.*, **97**:317, 1935.
- 56.* Morgagni, B.: The Seats and Causes of Diseases Investigated by Anatomy, vol. 1, translated by B. Alexander, London, 1769, A. Miller & T. Cadele, p. 808.
- 57.* Moritz, A. R.: Medionecrosis Aortae Idiopathicae Cistica, *Am. J. Path.* **717**, 1932.
- 58.* Nicholls, F.: *Phil. Tr. Roy. Soc. London*, **52**:265, 1763.
- 59.* Peacock, T.: Report on Cases of Dissecting Aneurysm, *Tr. Path. Soc. London*, **14**:87, 1862.
- 60.* Pekin, T. J., and Nesbitt, J. W.: Dissecting Aneurysm, *M. Bull. Vet. Admin.* **19**:96, 1942.
- 61.* Pennock, C. W.: Case of Anomalous Aneurysm of the Aorta Resulting From Effusion of Blood Between the Laminae Composing the Middle Coat of That Vessel, *Am. J. M. Sc.* **23**:2, 1838.
- 62.* Reich, N. E.: Dissecting Aneurysms; Clinico-Pathological Correlation of Nineteen Cases, *Clinics* **3**:346, 1944.

*Additional references to cases involving neurological manifestations, not specifically referred to in the text, and to several other important contributions.

- 63.* Rottino, A.: Medial Degeneration of the Aorta as Seen in Twelve Cases of Dissecting Aneurysm, *Arch. Path.* **28**:1, 1939.
- 64.* Rottino, A.: Medial Degeneration of the Aorta; A Study of 210 Routine Autopsy Specimens by a Serial Block Method. *Arch. Path.* **28**:377, 1939.
- 65.* Rottino, A.: Medial Degeneration, Cystic Variety, in Unruptured Aortas, *AM. HEART J.* **19**:330, 1940.
- 66.* Sailer, S.: Dissecting Aneurysm of the Aorta, *Arch. Path.* **33**:704, 1942.
- 67.* Todd, R. B.: Account of a Case of Dissecting Aneurysm of the Aorta, Innominata, and Right Carotid Artery, Giving Rise to Suppression of Urine and White Softening of the Brain, *Tr. Med. Chir. Soc. Edinburgh* **17**:301, 1844.
- 68.* Walker, C., and Walker, L.: Sudden Detachment of Aortic Intima (So-called Dissecting Aneurysm), *Brit. M. J.* **2**:200, 1919.
- 69.* Weiss, S.: The Clinical Course of Spontaneous Dissecting Aneurysm of the Aorta, *M. Clin. North America* **18**:1117, 1935.
- 70.* Weiss, S., Kinney, T. D., and Maher, M. M.: Dissecting Aneurysm of the Aorta With Experimental Atherosclerosis, *Am. J. M. Sc.* **200**:192, 1940.
- 71.* Wilson, I. H., and Halpern, D.: Dissecting Aneurysm of the Aorta; Antemortem Diagnosis, *Minnesota Med.* **24**:856, 1941.
- 72.* Wood, F. C., Pendergross, E. P., and Ostrum, H. W.: Dissecting Aneurysm of Aorta With Special Reference to Its Roentgenographic Features, *Am. J. Roentgenol.* **28**:437, 1932.
- 73.* Zions, M. A.: Dissecting Aneurysm, *Texas State J. Med.* **39**:375, 1943.

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MYOCARDITIS AND FRIEDREICH'S ATAXIA

A REPORT OF TWO CASES

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FRIEDREICH'S ataxia is usually considered an heredofamilial degenerative disease exclusively of the central nervous system, in which the posterior columns, the spinocerebellar pathways, and the pyramidal tracts of the spinal cord are predominantly involved. Degenerative changes in the cerebellum may be present, while morbid alterations in the midbrain and cerebrum occur more rarely. The association of a chronic, diffuse, nonspecific myocarditis with Friedreich's ataxia has received surprisingly scant attention in the American and English literature, considering the frequency with which such an association may be discovered to exist.

In 1863, Friedreich¹ published the first description of the disorder which now bears his name. Of the six patients whom he reported, five who were studied ante mortem presented abnormalities of cardiac mechanism. Post-mortem findings were recorded in three cases; in two of these subjects there were gross and microscopic changes interpreted as fatty degeneration. In the third subject there was diffuse cardiac hypertrophy associated with mitral and aortic valvular disease, suggestively rheumatic in origin. Newton Pitt,² in 1887, was the first to draw particular attention to deranged cardiovascular function in individuals with Friedreich's ataxia. Among the necropsy findings in his case there was definite microscopic evidence of a chronic myocarditis, with congestion, patchy granular degeneration, fibrosis, and round cell infiltration. Two cusps of the aortic valve were adherent, and the margins of all cusps were slightly irregular and calcareous. No other valvular deformities were described. In 1946 Russell³ collected from the French literature three additional cases of Friedreich's ataxia in which an interstitial myocarditis was found at autopsy. To these, she added four which came under her observation. Histopathologically, the process appeared to be chronic and progressive. Muscle destruction resulted from focal coagulative necrosis with collagenous tissue replacement, and there was compensatory hypertrophy of the surviving parenchymal fibers. Uneven, scanty interstitial infiltration with small lymphocytes and occasional polymorphonuclear

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Supported in part by a grant-in-aid from the H. H. Weinert Fund for Cardiovascular Research.

cells earmarked a low-grade inflammatory element. Ellwood⁴ recently reported a clinicopathologic study of two cases of Friedreich's ataxia with unusual cardiac complications. A diffuse interstitial myocardial fibrosis was found in one individual. The other manifested scarring of the mitral valve, slight atherosclerosis of the ascending aorta, and myocardial infarction; a true myocarditis was not reported in this patient.

From the clinical standpoint, abnormalities of cardiac mechanism and occasional terminal cardiac decompensation have been noted for eighty-five years in cases of Friedreich's ataxia. Such complications, frequently quite obscure in origin, have prompted several reports in French journals. There is a paucity of electrocardiographic studies of persons with Friedreich's disease, but those performed have yielded interesting results. Van Bogaert,⁵ in four of eight cases thus investigated, found definite evidence of myocardial damage. Two patients presented T_1 and T_2 inversions, while two presented negativity of T_2 and T_3 . In thirty-eight patients with Friedreich's disease, Evans and Wright⁶ found twelve distinctly abnormal tracings and ten with suggestive irregularities. The definite abnormalities were preponderantly those of T-wave inversion in Leads I and II, singly or in various combinations with one another or with a negative T_3 . There was a rather striking association of a positive family history of Friedreich's ataxia with abnormal electrocardiograms, and affected members of the same family tended to manifest similar electrocardiographic changes. Isolated case reports of electrocardiographic abnormalities associated with Friedreich's ataxia have appeared from time to time in the French literature.⁷⁻¹⁰

The etiology of the cardiopathy with which this disorder is occasionally attended is thoroughly obscure. The cardiac lesion has been attributed by some to degeneration of the vagal nuclei, resulting in sustained sympathetic hypertonia. Russell³ ventures a toxic cause, as microscopic examination of the vagal nuclei in her patients disclosed no significant changes. It is difficult to visualize autonomic imbalance as a potential cause of a true myocarditis. If the cause be a toxin, its source remains as yet unidentified. In the foregoing case reports of Friedreich's disease associated with myocarditis, no significant inflammation was found in other organs, and it was not possible to demonstrate a possible focus of infection at necropsy. And whether or not an identical noxious agent is responsible for both the myocardial and central nervous system lesions is purely speculative.

We have recently had an opportunity to observe two patients with Friedreich's ataxia, in whom conspicuous clinical and electrocardiographic cardiac aberrations were apparent. A pathologic study was accomplished in one. The rarity with which the condition has been described seems to warrant the following case reports.

CASE REPORTS

CASE 1.—P. T., a 27-year-old Mexican man, was admitted to the State Psychopathic Hospital on July 24, 1947. The onset of the neurological disorder was dated to 1936, when the patient was struck on the right hip by a car. Subsequently he gradually developed weakness, poor coordination, and wasting of both legs. He had become unable to walk, and was incapacitated for work.

He had noted irregular heart action and palpitation since January, 1947. A communication from the family physician indicated that on June 2, 1947, the patient developed auricular fibrillation, with a fall of the arterial blood pressure to 60/0. At this time quinidine and digitalis were administered, and the blood pressure on June 16 was 130/70. In the history there was evidence neither of congenital heart disease nor of rheumatic fever. Family history was negative for similar illnesses.

The physical examination revealed a chronically ill man whose temperature was 99.0° F.; pulse rate, 100 per minute; respiratory rate, 20 per minute; and blood pressure, 100/80. Scattered moist râles were heard throughout both lungs. The heart was enlarged to about 3 cm. beyond the left midclavicular line in the fifth intercostal space. The rhythm was grossly irregular,

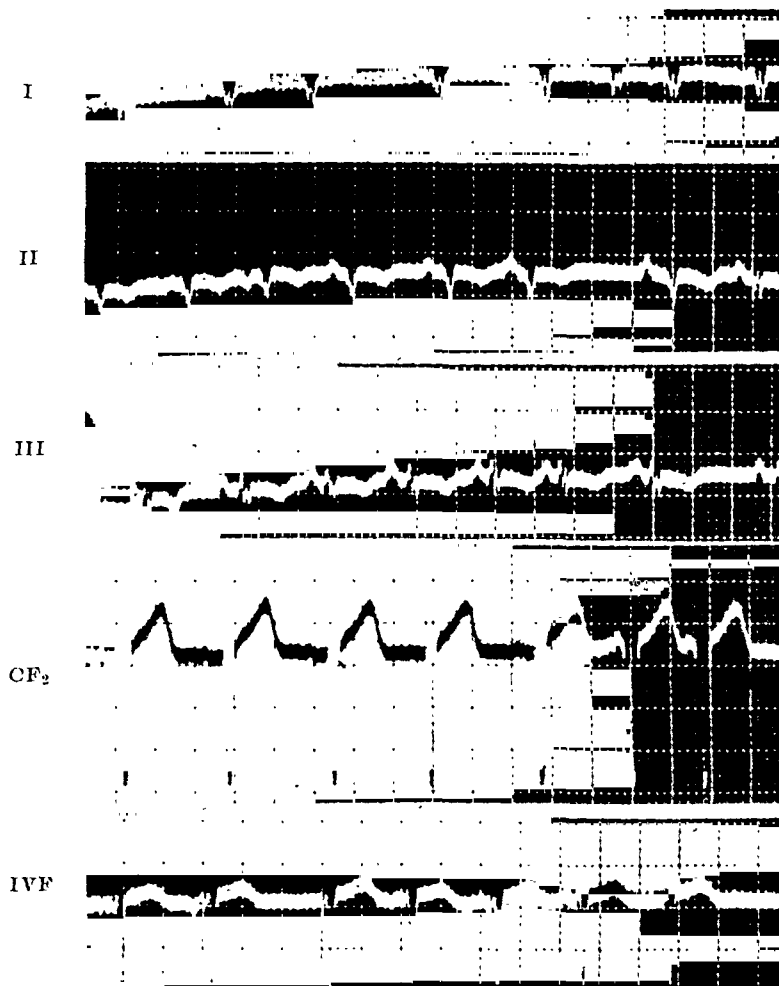


Fig. 1.—Electrocardiogram in Case 1 (P. T.), July 31, 1947, taken after reversion to sinus tachycardia, rate 110. Right axis deviation is present, and there are frequent supraventricular ectopic beats. Q_1 and Q_2 are deep, and QRS complexes are markedly notched in the limb leads. The T wave is flat in Lead I and negative in Leads II and III.

and rate at the apex was 140 per minute, compared with 100 at the wrist. There was a low-pitched apical murmur heard in early and middle diastole. The second pulmonary sound was loud and reduplicated. The speech had a halting, explosive quality. The muscles of the extremities were flaccid and atrophic. All movements were poorly executed, and marked ataxia was noted during tests for coordination. There was scoliosis of the thoracic vertebrae with the convexity to the right. A bilateral pes cavus was present and the deep, tendon reflexes were absent in the lower extremities. No pathologic reflexes were elicited. There was definite impairment of all modalities of sensation in the lower extremities. Cranial nerves were intact.

The laboratory studies revealed a red cell count of 4.66 million with 97 per cent hemoglobin. The white cells numbered 11,500 per cubic millimeter, and the differential count was essentially normal. Urinalysis revealed a specific gravity of 1.027, a trace of protein, and no sugar; microscopic examination revealed no abnormal constituents; blood Kahn and Kolmer tests were negative. Examination of the spinal fluid disclosed no abnormalities. The electrocardiogram (Fig. 1) revealed frequent supraventricular ectopic beats, with right axis deviation (axis 138°), and definite evidence of myocardial damage. Phonocardiographic study (Fig. 2) confirmed the presence of the apical diastolic murmur.

During hospitalization the patient was given nutritional support and physiotherapy. Since he showed no signs of cardiac decompensation, no cardiotonic drugs were administered. Two twenty-four hour courses of oral quinidine sulfate were given; a total dose of 1.0 Gm. on July 24, and a total dose of 1.5 Gm. on July 29. The second course succeeded in reverting the circus mechanism to sinus rhythm. On September 5 the patient complained of moderate epigastric pain and nausea. The symptoms soon disappeared, and the general condition remained about the same. At 5 A.M. on September 6 the patient suddenly vomited copious quantities of previously ingested food, and expired before emergency measures could be inaugurated.

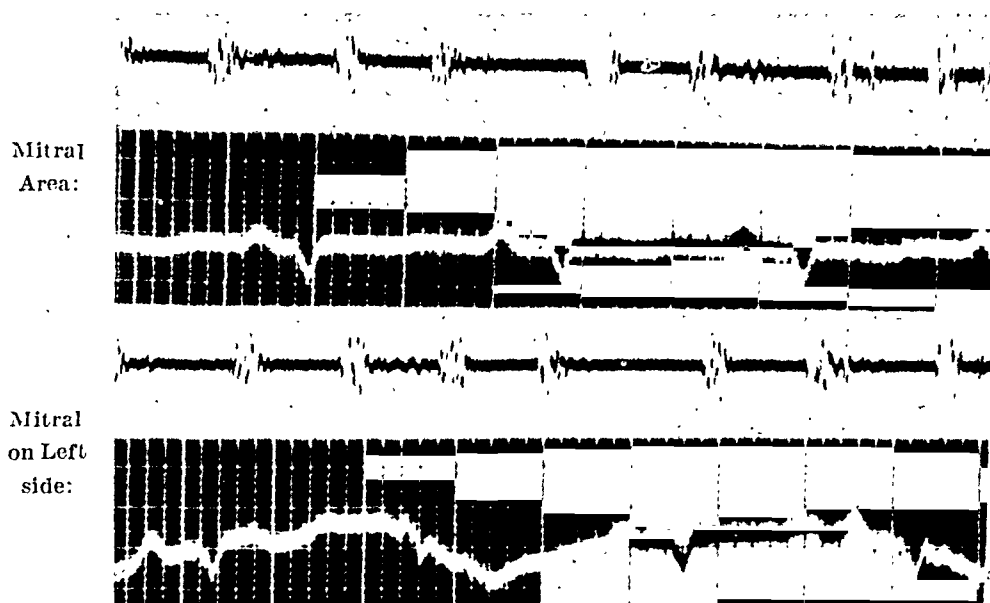


Fig. 2.—Phonocardiogram in Case 1, taken at same time as Fig. 1. The top tracing demonstrates the low-pitched apical murmur beginning immediately after the second sound and lasting through the middle of diastole. The bottom tracing shows a similar apical murmur with the patient recumbent on his left side.

Pathologic Findings.—At autopsy several points of interest relative to the clinical course were noted. The heart weighed 550 grams, and the epicardium was speckled with many small petechiae, which were most noticeable on the left ventricle and left atrium. The myocardium was reddish-brown in color, and in places was soft in consistency. The left ventricular wall measured 17 mm. in thickness, and the right measured 7 mm. in thickness. Both ventricular cavities were dilated. The endocardium was smooth, but there were several small grayish-red clots adherent to the apex of the left ventricle. The valve leaflets showed no gross abnormality. The coronary arteries showed no atherosclerosis, and no evidence of thrombosis or occlusion was found throughout their course. Microscopically the myocardium showed a diffuse interstitial fibrosis (Figs. 3 and 4). The myocardial fibers varied in size, and were rather widely separated by many strands of delicate fibrous connective tissue. Many of the fibers appeared larger than normal (Fig. 4). In some places there were a few lymphocytes and plasma cells scattered through the fibrous tissue.

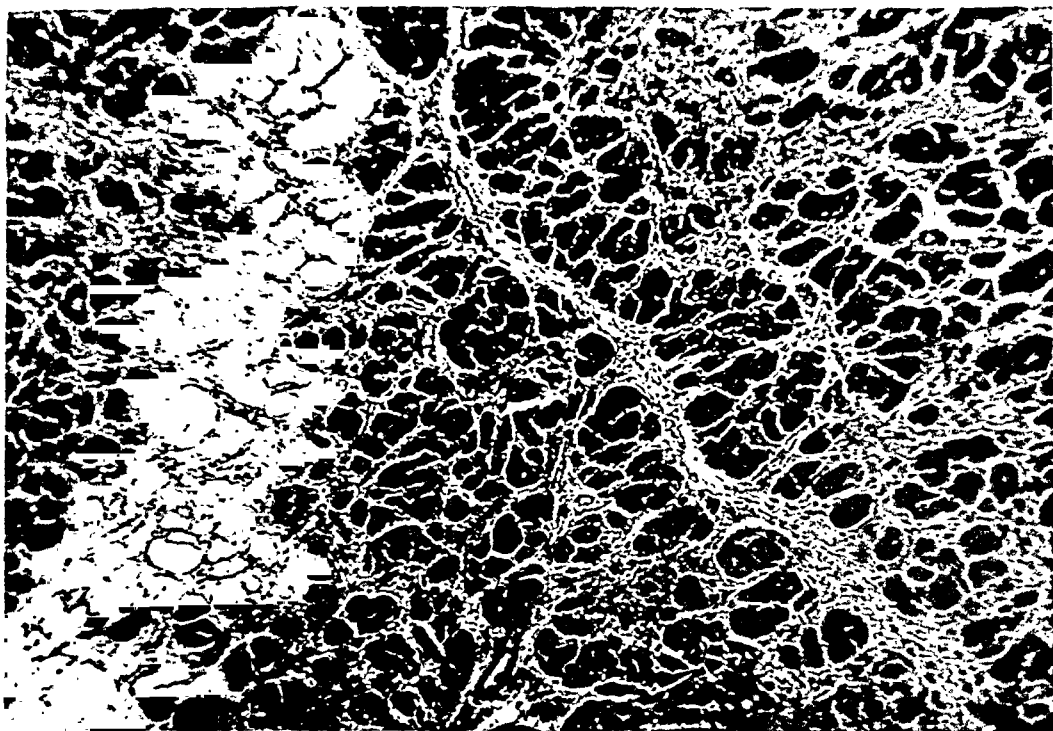


Fig. 3.—Section of myocardium in Case 1, under low magnification. Note the areas of degenerating myocardium with replacement by fibrous tissue. Some of the remaining muscle fibers show hypertrophy. The section is representative of the entire myocardium. (Hematoxylin and eosin stain, $\times 53$.)

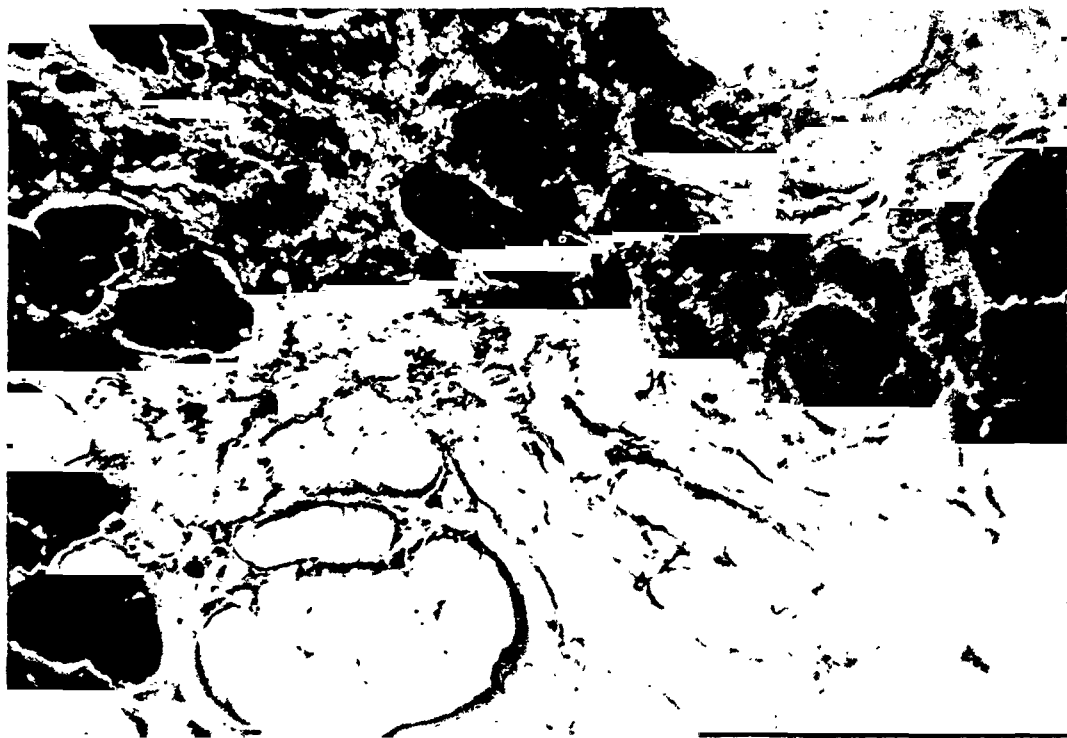


Fig. 4.—High-power magnification of the heart muscle in Case 1. The diffuse fibrosis enveloping the degenerating muscle fibers is conspicuous. Occasional small round cells can be seen. (Hematoxylin and eosin stain, $\times 300$.)

The lungs weighed 1,150 and 950 grams, and on sectioning considerable pink fluid escaped from the cut surface. Microscopically, they showed pulmonary edema and many pigment-laden macrophages. The liver weighed 1,400 grams and showed slight chronic passive congestion. The right kidney weighed 150 grams, and the left weighed 170 grams. There was a small, old, stellate scar present on the cortex of the left kidney. There were no pathologic changes in the arterioles or glomeruli.

The brain weighed 1,450 grams and grossly showed no abnormality. The spinal cord was markedly flattened and thin in the anteroposterior dimensions. Grossly the cut section showed the dorsal columns to be thin and small. Microscopically the sections showed degeneration of the fasciculus gracilis, fasciculus cuneatus, and the dorsal spinocerebellar tracts. There was present considerable glial tissue with a whorled appearance, particularly in the fasciculus gracilis. No microscopic changes were noted in the cerebral hemispheres or in the cerebellum. Serial sections were not taken to demonstrate the vagal nuclei in their entirety, but no lesions were noted in this area.

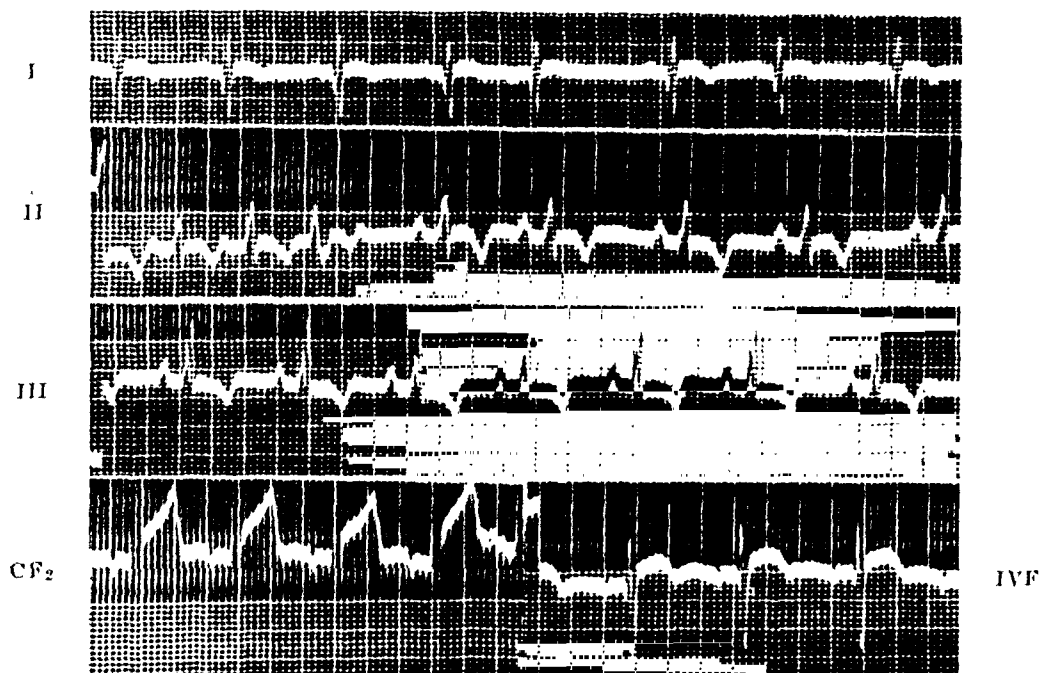


Fig. 5 A.—Electrocardiogram in Case 2 (C. H. C.), April 29, 1948. There is sinus rhythm at a rate of 88, with frequent atrial ectopic beats. A 2.0 mm. Q wave is present in Lead I, and a 1.0 mm. Q wave in Lead IVF. There is negativity of T₁, T₂, and T₃, and the RS-T segments are elevated in Leads CF₂ and IVF.

CASE 2.—C. H. C., a 28-year-old white man, was admitted to the State Psychopathic Hospital on March 19, 1947, and was hospitalized intermittently until June 1, 1948. Onset of symptoms was at the age of 14, when, following a fracture of the left leg, he failed to recover normal function despite good union. He noted progressive weakness of his legs, and several years later the weakness involved the arms and hands. For several months there had been numbness and tingling of the legs, feet, and hands. His speech became slower and scanning, and he had increasing awkwardness in writing. A tremor of the hands and feet was noted whenever he attempted to perform any act. The patient had been confined to a wheelchair since admission. There had been noted some dyspnea upon moderate exertion, but no other symptoms referable to the heart. There was no history of chorea, of prolonged fever, or of migratory polyarthritis. Several members of the family had high-arched feet similar to those of the patient, but there was no family history of mental or nervous illness.

On physical examination the patient was seen to be sthenic in habitus, and in no acute distress. The sensorium was clear, but speech was slow and slurred. Temperature was 98.6° F.; pulse rate, 100 per minute; respiratory rate, 20 per minute; and blood pressure, 130/80. The chest showed marked scoliosis with convexity to the right. The lungs appeared normal. The cardiac apical impulse was palpable in the fifth intercostal space, inside the midclavicular line. The heart was not enlarged, and contour appeared normal to percussion. There were no shocks or thrills. The heart tones were of fair quality, and occasional premature contractions were noted. Upon tachycardia induced by exercise, a short, low-pitched presystolic murmur was heard at the apex. No other murmurs were present. The second aortic and pulmonic sounds were equal in intensity. Abdomen, genitalia, and rectum were normal. There were high-arched feet bilaterally. Neurological examination showed that the patient was markedly ataxic, and unable to stand alone. Muscle strength of the upper and lower extremities was decreased. There was a generalized atrophy of the muscles of the lower extremities. A slow, coarse intention tremor involved all extremities. All coordinated movements were done with extreme difficulty. Deep reflexes of the upper extremities were markedly hypoactive, and patellar and ankle jerks could not be elicited. A bilateral positive Babinski sign was present. Abdominal and cremasteric reflexes were absent. Sensation to pain, touch, and temperature was intact. In the lower extremities, there was marked impairment of position and vibratory sensation. Nystagmus was present on right and left lateral gaze, but no other cranial-nerve abnormalities were elicited.

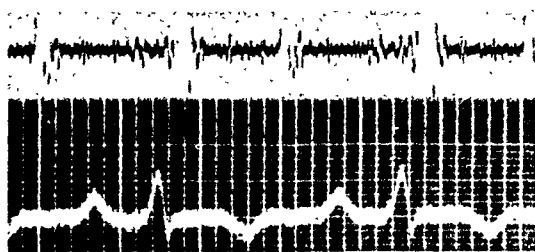


Fig. 5 B.—Phonocardiogram in Case 2 confirms the short apical presystolic murmur heard only during tachycardia.

Laboratory studies showed a red cell count of 5.32 million with 17.0 grams of hemoglobin. The white cell count was 10,600 per cubic millimeter, with a normal differential count. Urinalysis showed a specific gravity of 1.025, acid reaction, a faint trace of protein, and no sugar; microscopic examination showed no abnormal constituents. Reactions to blood Kahn and Kolmer tests were negative. An electroencephalogram, as well as skull and chest films, showed no abnormality. The spinal fluid was normal. An electrocardiogram (Fig. 5 A) showed marked alterations, and the phonocardiogram (Fig. 5 B) verified the presystolic murmur at the apex.

DISCUSSION

Despite the absence of a rheumatic history in Case 1, the diastolic apical murmur and atrial fibrillation strongly suggested the presence of mitral stenosis. However, the clinical suspicion of rheumatic heart disease was not substantiated at necropsy. The absence of valvular lesions was a striking finding, and exhaustive search failed to reveal any microscopic evidence that the myocardial changes were rheumatic in origin. The coronary arteries were widely patent, and showed no areas of atherosclerosis. Although the tracing in Fig. 1 shows only supra-ventricular ectopic beats, another tracing on this patient showed frequent impulses of ventricular origin. A sudden mechanism disorder such as ventricular fibrillation was considered the probable cause of the sudden death.

The microscopic appearance of the myocardium was similar to that described by Pitt² in a patient with Friedreich's ataxia, and by Russell³ in her fourth case. There was collagenous tissue replacement of degenerating myocardium, with hypertrophy of some of the remaining muscle fibers. The diffuse fibrosis was prominent, with infiltration by a few small round cells. No acute necrotic changes were observed in the myocardium. There was a notable absence of the fatty degeneration described in some of the cases previously reported.

The clinical findings in Case 2 indicated that in all probability the cardiac lesion was also a myocarditis of the type associated with Friedreich's ataxia. There had been no episodes suggestive of rheumatic fever, and no symptoms or signs pointed to disease of the coronary arteries. The presystolic apical murmur was not conspicuous, and was heard only upon acceleration of the heart rate.

The electrocardiograms show marked abnormalities, and frequent auricular ectopic beats are present. There is a similarity in that both tracings show inversion of T₂ and T₃. In Case 2 the configuration in Lead I and Lead IVF was considered to be due to subepicardial involvement anteriorly. Several serial tracings taken over a period of three months showed no change, and there were no symptoms suggestive of a myocardial infarct.

Diastolic murmurs have been previously reported in patients with Friedreich's ataxia. The patient described by Pitt² had at the apex a "bruit, doubtfully presystolic," and at necropsy no mitral lesion was demonstrable. Debasch, Calo, and Almanza⁹ noted an apical presystolic murmur in a patient with Friedreich's ataxia, and two patients observed by Van Bogaert⁵ had protodiastolic murmurs on exertion. Marked dilatation of the left ventricle relative to the mitral orifice is considered the most likely mechanism underlying the murmur heard in Case 1, as there was no necropsy evidence of valvular disease. Although mitral valvulitis cannot be excluded in the living patient, the fact that the murmur is heard only during tachycardia emphasizes the importance of the velocity of blood flow in its production. The functional aspect of certain apical diastolic murmurs has been stressed by Bramwell¹¹ and by Dechard and Beard.¹²

The frequent presence of myocarditis in Friedreich's disease appears to be well established, although its cause remains obscure. The rarity of its observation may well be due to failure to investigate this association. It seems to us that the diagnosis of Friedreich's ataxia should demand a thorough evaluation of the cardiac status. Limitation of activity and supportive measures may result in prolongation of life in patients in whom there is evidence of cardiopathy.

SUMMARY

The literature concerning myocarditis in Friedreich's ataxia is briefly reviewed.

Two cases of Friedreich's ataxia with marked electrocardiographic changes and apical diastolic murmurs are presented. Necropsy findings in one patient showed a diffuse interstitial myocarditis with nothing to identify a specific etiological basis. Both are presumed to be of the type associated with Friedreich's ataxia.

It is concluded that a thorough cardiac study is indicated in patients with Friedreich's disease.

The authors desire to express their appreciation to Jack R. Ewalt, M.D., Professor of Neuropsychiatry, for making this clinical material available; and to George R. Herrmann, M.D., for his aid and encouragement.

REFERENCES

1. Friedreich, N.: Ueber degenerative Atrophie der spinalen Hinterstränge, *N. Arch. path. Anat.* **26**:391, 433, 1863.
2. Pitt, G. Newton: On a Case of Friedreich's Disease. Its Clinical History and Post-mortem Appearances, *Guy's Hosp. Rep.* **44**:369, 1887.
3. Russell, Dorothy S.: Myocarditis in Friedreich's Ataxia, *J. Path. & Bact.* **58**:739, 1946.
4. Ellwood, Walter W.: Friedreich's Ataxia With Unusual Heart Complications, *California Med.* **68**:296, 1948.
5. Van Bogaert, A., and Van Bogaert, L.: Concerning the Electrocardiographic Alterations in Friedreich's Disease, *Arch. d. mal. du coeur* **29**:630, 1936.
6. Evans, William, and Wright, Gordon: The Electrocardiogram in Friedreich Disease, *Brit. Heart J.* **4**:91, 1942.
7. Rathery, F., Mollaret, P., and Sterne, J.: Sporadic Case of Friedreich's Disease With Cardiac Arrhythmia and Cheyne-Stokes Respiration, *Bull. et mém. Soc. et méd. d. hôp. de Paris* **50**:1382, 1934.
8. Guillian, G., and Mollaret, P.: Friedreich's Disease With Progressive and Solitary Electrocardiographic Alterations, *Bull. et mém. Soc. méd. d. hôp. de Paris* **50**:1577, 1934.
9. Debbasch, G., Calo, A., and Almanza, G.: Sporadic Case of Friedreich's Disease With Heart Disease and Disturbances of Somatic Development, *Arch. d. mal. du coeur* **28**:529, 1935.
10. Debré, R., Marie, J., Soulié, P., and de Font-Réaulx, P.: Coronary Type of Electrocardiogram in Child With Friedreich's Disease, *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:749, 1936.
11. Bramwell, Crichton: Signs Simulating Those of Mitral Stenosis, *Brit. Heart J.* **5**:24, 1943.
12. Dechard, George M., Jr., and Beard, Owen W.: Functional Mitral Diastolic Murmurs, *Texas Rep. Biol. & Med.* **4**:119, 1946.

PULMONARY HEMANGIOMA WITH PULMONARY ARTERY-AORTIC SEPTAL DEFECT

ATTEMPTED ROENTGEN VISUALIZATION BY CATHETERIZATION OF BRACHIAL ARTERY AND BASILIC VEINS

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DESPITE the fact that pulmonary hemangioma (arteriovenous fistula) is rarely encountered, this lesion assumes practical importance because of its curability by surgical means. Every effort should be made to establish the diagnosis, since delay in treatment may lead to pulmonary hemorrhage and death. The present case report illustrates such a catastrophe, in spite of the fact that the lesion was suspected and attempts were made to demonstrate it roentgenographically by both venous and arterial catheterization. This case is unique in that the patient also had a pulmonary artery-aortic septal defect.

CASE REPORT

J. P., a 20-year-old white man, was admitted to Jefferson Hospital on July 31, 1945. The essential features of his illness consisted of the presence of clubbing of the fingers and toes for fifteen years; cyanosis of the lips, fingers, and toes for ten years; dyspnea on exertion for ten years; pain in the left chest for the two months preceding admission; and two episodes of hemoptysis during the two months preceding admission.

There was no family history of congenital heart disease. The patient's mother had been treated for syphilis during the pregnancy; she had never had German measles.

At birth the patient was not a "blue baby." Cyanosis first became evident when the patient was about 4 years old, at which time a diagnosis of Ayerza's disease was suggested. The patient was studied at Hazleton State Hospital, Hazleton, Pa., and found to have a systolic murmur over the pulmonary artery, but no thrill. Roentgenograms of the chest revealed no enlargement of the heart, but the presence of a small shadow in the left upper lung, not associated with any hilar changes. The electrocardiogram revealed right axis deviation. The patient was studied many times during the following fifteen years, but the same findings persisted: absence of heart enlargement, normal pulse and blood pressure, inconstant systolic pulmonary murmur, accentuated second pulmonary sound, and an area of increased density in the upper left lung without hilar enlargement. The patient was sent to Jefferson Hospital by two of us (F. V. P. and J. F.) with the diagnosis of congenital heart disease and hemangioma of the lung.

Physical examination revealed the patient to be well developed physically and his nutritional status appeared good. Temperature, pulse, respirations, and blood pressure were normal. The abnormal physical findings were as follows: (1) cyanosis of face, lips, hands, and feet; (2) clubbing of fingers and toes; (3) thrill over the entire anterior chest wall; (4) dullness on percussion over an area just to the left of the aortic arch; (5) a loud, crescendo systolic murmur heard best over the pulmonic area but transmitted to the neck, left axilla, entire left chest, and to a lesser degree to the right chest.

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Blood studies revealed hemoglobin levels varying from 130 to 150 per cent, red blood cell counts from 7.1 to 8.3 million, hematocrit from 73 to 75, white blood cell counts from 5,000 to 11,000, and platelets from 60,000 to 150,000. A representative differential count was: polymorphonuclear cells, 86 per cent; basophiles, 1 per cent; lymphocytes, 11 per cent; and monocytes, 2 per cent. Examination of the sternal bone marrow revealed normal marrow hyperplasia but a distinct elevation in the percentage of normoblasts from a normal of 20 per cent to a level of 33 per cent. The sedimentation rate was found to be normal on three occasions. Repeated urinalyses, as well as kidney and liver function tests, were normal.

Roentgenograms of the chest (Figs. 1 and 2) revealed an oval shadow of increased density in the left upper lobe. The mass appeared homogeneous, had a smooth contour, and did not pulsate. The heart was normal in size, shape, and position. A test of swallowing function with barium revealed that the pulmonary mass was not located near the esophagus or the aorta. Lateral views of the thoracic and lumbar spine showed no abnormality of the vertebral bodies or their intervening spaces.



Fig. 1.—Plain roentgenogram of chest (anteroposterior view), showing oval shadow of arteriovenous aneurysm in left upper lobe.

The electrocardiogram showed marked right axis deviation, with notching and spreading of the P waves, suggesting auricular enlargement.

Bronchoscopy revealed definite narrowing of the left main bronchus due to encroachment on the anteroposterior diameter, so that the lumen of the bronchus presented its greater diameter in the coronal plane.

On Aug. 9, 1945, pulmonary arteriography was attempted. With local anesthesia, No. 8 F ureteral catheters were inserted (by F. B. W.) into the basilic veins of both arms and threaded under fluoroscopic guidance through the axillary and subclavian veins and superior vena cava into the right atrium. A scout film was then made, which showed the catheters in place. With the patient in proper position, 10 c.c. of 70 per cent Diodrast were injected simultaneously through each catheter, and two films of the chest were made at a two-second interval. These films showed

the right atrium and ventricle to be well filled, with dye passing through the pulmonary artery and out through the right and left pulmonary arteries into the small branches of each lung (Fig. 3). The branches surrounding the mass in the left upper lung were well visualized. The fact that at no time was any Diodrast seen in the left side of the heart or aorta on these films ruled out dextro-position of the aorta. The patient was then turned to a partial left anterior oblique position. A full oblique position was not obtainable because of the necessary placement of the arms. Again 10 c.c. of Diodrast were injected simultaneously through each catheter, and two exposures were made in quick succession. These films showed the right atrium, the right ventricle, and the pulmonary artery and its two main branches very well. Again there was no evidence of any opaque medium in the left ventricle or aorta. The outstanding feature demonstrated by these tests was a distinct dilatation of the pulmonary artery.



Fig. 2.—Lateral view of pulmonary arteriovenous aneurysm.

On Aug. 23, 1945, thoracic aortography was attempted. With the patient under local anesthesia, the right radial and ulnar arteries were exposed at their origin from the brachial artery. The radial artery was opened about one-fourth of an inch from its origin, and a No. 8 F ureteral catheter was quickly introduced upward through the brachial and subclavian arteries. Because of spasm of the artery about the catheter there was no leakage of blood at the site of introduction, but considerable force had to be exerted to advance the catheter. Under fluoroscopic vision it was noted that the catheter passed from the innominate artery into the common carotid. By elevating the patient's arm and rotating the catheter, it was possible to introduce it into the aorta and left ventricle. Ten cubic centimeters of 70 per cent Diodrast were injected through the catheter, and two films were taken at a two-second interval, starting immediately at the completion of injection. Unfortunately, the amount of Diodrast which could be injected through the catheter was too small to give clear definition of the aorta. Again 10 c.c. of Diodrast were injected, and two additional films were taken, as before. On one film there was faint visualization of the aorta, which was interpreted as showing evidence of some hypoplasia (Fig. 4).



Fig. 3.—Pulmonary arteriogram, showing relation of mass in left upper lobe to the vessels.



Fig. 4.—Attempted aortogram, by retrograde arterial catheterization.

The catheter remained in place about one-half hour, at the end of which time the right arm and hand were somewhat cooler than the left. On removal of the catheter, the radial artery was ligated on either side of the opening. Two hours later the right arm and hand were only slightly cooler than the opposite members, and no radial pulse was palpable at the wrist. Two days later both upper extremities were of equal warmth and a faint but definite radial pulse could be felt.

The patient was discharged on Sept. 4, 1945. He was advised to return for surgery, but because he felt well, he would not give consent to an operation. On May 11, 1947, the patient exerted himself unduly by pushing a stalled automobile. Within one hour he collapsed as a result of a large pulmonary hemorrhage, and was taken to the Hazleton State Hospital in a critical condition. In spite of all supportive measures, he expired. A post-mortem examination was performed.



Fig. 5.—Heart specimen, showing large foramen between aorta and pulmonary artery.

Post-mortem Findings (Hazleton State Hospital).—There was about 1.0 liter of free and clotted blood within the left pleural cavity, while none was present in the right. The left lung was of a dark bluish-red color, suggesting infiltration with blood throughout. With application of pressure to the midportion of the upper lobe, the pleural surface became raised at a point of apparent rupture, and a large amount of dark brown free and clotted blood escaped. On cut section, the left lung appeared hemorrhagic throughout, and the origin of the hemorrhage could be traced to a large, V-shaped, widened, cystic-like space filled with blood. The left lung had a weight of $3\frac{1}{8}$ pounds, as compared with $1\frac{1}{2}$ pounds for the right lung. There was slight hemorrhagic infiltration in the middle and upper lobes of the right lung.

Examination of the heart revealed a markedly hypertrophied right ventricle. On section, the right ventricle measured 2.5 cm. in thickness, as compared with a thickness of 1.5 cm. for the left ventricle. When the cardiac chambers and great vessels were opened, there was found a large oval communication between the aorta and pulmonary artery (Fig. 5). This foramen measured 3.2 cm. in its vertical diameter and 2.1 cm. in its horizontal diameter. The inferior margin of the foramen was 0.9 cm. above the upper free margin of the pulmonary valves and 0.1 cm. above the aortic valves. The intima was intact. All the valves were normal. There were no septal defects in the atria or ventricles.

Histologic examination of the left lung revealed extensive hemorrhages in all of the sections examined, with dilatation of the capillaries and marked hypertrophy of the medium-sized vessels. Tissue removed from the vicinity of the cystic spaces, at the origin of the rupture, revealed an irregular, cavernous appearance of the blood vessels, with papillary formation, as is seen in cavernous hemangioma.

The liver and spleen contained miliary granulomata.

DISCUSSION

The amenability to diagnosis and the ease of cure by surgery of pulmonary arteriovenous fistula have been the stimulus for an increasing number of reports of this rare lesion. The few case reports in the literature, however, warrant the accumulation of all available data in order to arrive at a more thorough understanding of this problem. For this reason the cases reported to date¹⁻¹⁶ are summarized in Table I.

Highly valid statistical data cannot be derived from the eighteen cases reported, but certain features seem outstanding. The condition is predominant in men. Although the lesion is congenital, the symptoms and signs usually do not become pronounced until the beginning of the third decade. Details of symptomatology and roentgenologic diagnosis have been adequately discussed in recent articles. The characteristic syndrome consists of cyanosis, clubbing of the fingers and toes, and polycythemia without abnormality of the heart; roentgenologic study reveals a lobulated mass of uniform density which may or may not pulsate under fluoroscopic observation. Either lung, or both lungs, may be involved, and the lesions are frequently multiple. Effective therapy consists in surgical extirpation of the involved portion of the lung, by lobectomy, pneumonectomy, or local excision. Ligation of the "feeder" artery may also result in improvement in properly selected cases. As in the case reported here, medical treatment is little more effective than no treatment at all, and the patient eventually will probably suffer a fatal pulmonary hemorrhage.

A noteworthy feature in the case reported here was the large foramen between the aorta and pulmonary artery. Such a defect must in itself be extremely rare, since Abbott¹⁷ lists only ten analyzed cases of "communication between aorta and pulmonary artery" in her 1,000-case analysis, and White¹⁸ and Taussig¹⁹ list no additional cases. This lesion apparently represents an unusual variety of partial truncus arteriosus, in which the division of the aorta and pulmonary artery is incomplete but in which there is normal development of all the valves.

Since the effective pulmonary flow is decreased in the presence of a pulmonary arteriovenous fistula, it is logical to suppose that the communication between the aorta and pulmonary artery in this patient represented an attempt on the part of nature to overcome this circulatory handicap. It is evident that the shunt

TABLE I. CLINICAL FINDINGS, TREATMENT, AND RESULTS IN EIGHTEEN PREVIOUSLY REPORTED CASES AND IN THE PRESENT ADDITIONAL CASE OF PULMONARY ARTERIOVENOUS FISTULAS

AUTHORS	AGE AND SEX	CYANOSIS	CLUBBING	DYSPNEA	HEMOPTYSIS	BRUIT	CARDIAC ENLARGEMENT	POLYCYTHEMIA	ROENTGENOGRAM	LUNG INVOLVED	LESIONS	SURGICAL TREATMENT	RESULTS
Wilkins, 1917 ¹	23, F.	+		+	+	+	+		+	R, L	3	0	Fatal hemorrhage; necropsy
Bowers, 1936 ²	2 days, M.	0	0	0	0	0	0			L		0	Died
Rodes, 1938 ³	25, M.	+	+	+	+	0	0	+	+	R, L	3	0	Fatal hemorrhage; necropsy
Smith and Horton, 1939 ⁴	46, M.	+	+	+	0	+	0	+	+	R	1	0	Living, 1946
Hepburn and Dauphinee, 1942 ⁵	23, F.	+	+	+	0	0	0	+	+	R	1	Pneumectomy	Living and well
Goldman, 1943 ⁶	22, F.	+	+	+	0	+	0	+	+	L	1	0	Unimproved
Adams, Thornton, and Eichelberger, 1944 ⁷	24, M.	+	+	0	+	0	0	+	+	L	2	Pneumectomy	Living and well
Jones and Thompson, 1944 ⁸	24, M.	+	+	0	0	+	0	+	+	R	1	Pneumectomy	Living and well
Janes, 1944 ⁹	30, M.	+	0	0	+	+	0	0	+	R, L	3	Local excisions	Improved
Sisson, Murphy and Newman, 1945 ¹⁰	45, F.	+	+	+	+	+	+	+	+	R, L	2	0	Died, necropsy
Alexander, 1945 ¹¹	41, M.	+	+	+	0	+		+	+	R, L		0	Died; coronary thrombosis
Makler and Zion, 1946 ¹²	20, M.	+	+	+	0	+	0	+	+	R, L	4	0	Unimproved
Beierwaltes and Byron, 1947 ¹³	27, F.	+	+	+	0	0	0	+	+	R	1	Lobectomy	Living and well
Burchell and Claggett, 1947 ¹⁴	20, M.	+	+	0	0	+	0	+	+	R	1	Lobectomy	Living and well
Watson, 1947 ^{15a}	27, M.	+	0	0	0	0	0	0	+	R	1	Ligation of "feeder" artery	Improved
Watson, 1947 ^{15b}	21, M.	+	+	+	0	0	0	+	+	R	1	Lobectomy	Living and well
Bisgard, 1947 ¹⁶	29, M.	+	+	+	0	+	0	+	+	R	1	Lobectomy	Living and well
Authors' case	20, M.	+	+	+	+	+	0	+	+	L	1	0	Fatal hemorrhage; necropsy

of blood from aorta to pulmonary artery produced pulmonary hypertension, as shown by the marked hypertrophy of the right ventricle at necropsy. This hypertension, however, rendered the patient's involved lung more susceptible to rupture. In addition, the shunt of blood from the aorta apparently became insufficient to overcome the reduction of effective pulmonary flow, since the patient developed polycythemia.

It is probable that this patient would have benefited from extirpation of the portion of lung bearing the arteriovenous fistula. The circulatory physiology would probably have reverted then to that obtaining in patent ductus arteriosus. Since the communication between aorta and pulmonary artery was not suspected during life, the postoperative result might have been confusing, indeed. Whether the large foramen could have been closed by operative intervention, had it been diagnosed and the procedure deemed beneficial, is a matter of the greatest conjecture.

The results of angiography by catheterization were disappointing in this patient. The information gained by the arterial catheterization hardly warranted the risk. Moreover, some of the findings were falsely interpreted. Some of the contrast medium injected into the left ventricle flowed through the pulmonary artery-aortic septal defect and into the lungs, thereby reducing the amount that should have gone into the aorta, which suggested an interpretation of hypoplastic aorta. The lumen of the catheter was too small to allow sufficiently rapid injection of the contrast medium. It is now definitely established that the Robb-Steinberg technique²⁰ of angiocardiology is the method of choice. However, in congenital heart disease, catheterization of the heart may yield valuable information when intracardiac pressures are taken and chemical analyses (oxygen tension of blood) made.

SUMMARY AND CONCLUSIONS

1. A case of pulmonary arteriovenous fistula associated with pulmonary artery-aortic septal defect is presented and discussed. The associated defect calls attention to the fact that other congenital vascular abnormalities should be looked for in patients with pulmonary arteriovenous aneurysms.

2. Attempted angiography by venous and arterial catheterizations proved interesting, but the Robb-Steinberg method would probably have been safer and more informative.

3. In the case presented, fatal pulmonary hemorrhage occurred as a result of delay in surgical intervention.

Since this article was submitted for publication, L. Dexter (Modern Medicine, February 15, 1949, p. 96) has reported that on one occasion aortic septal defect has been demonstrated by passage of the right heart catheter from the pulmonary artery into the aorta, but that in other suspected cases this could not be accomplished.

In addition, since this paper was submitted for publication, one of the authors (F.B.W.) performed angiocardiology by the Robb-Steinberg method on an additional patient suspected of having pulmonary hemangioma, with conclusive demonstration of the lesion in the right lung. Surgical therapy is planned.

REFERENCES

1. Wilkens, G. D.: Ein Fall von Multiplen Pulmonalisaneurysm, Beitr. z. Klin d. Tuberk. **38**:1, 1917.
2. Bowers, W. F.: Rupture of Visceral Hemangioma as Cause of Death; With Report of a Case of Pulmonary Hemangioma, Nebraska M. J. **21**:55, 1936.
3. Rodes, C. B.: Cavernous Hemangiomas of the Lung With Secondary Polycythemia, J. A. M. A. **110**:1914, 1938.
4. Smith, H. L., and Horton, B. T.: Arteriovenous Fistula of the Lung Associated With Polycythemia Vera: Report of a Case in Which the Diagnosis Was Made Clinically, AM. HEART J. **18**:589, 1939.
5. Hepburn, J., and Dauphinee, J. A.: Successful Removal of Hemangioma of the Lung Followed by the Disappearance of Polycythemia, Am. J. M. Sc. **204**:681, 1942.
6. Goldman, A.: Cavernous Hemangioma of Lung; Secondary Polycythemia, Dis. of Chest **9**:479, 1943.
7. Adams, W. E., Thornton, T. F., Jr., and Eichelberger, L.: Cavernous Hemangioma of the Lung (Arteriovenous Fistula); Report of a Case With Successful Treatment by Pneumonectomy, Arch. Surg. **49**:51, 1944.
8. Jones, J. C., and Thompson, W. P.: Arteriovenous Fistula of Lung; Report of Patient Cured by Pneumonectomy, J. Thoracic Surg. **13**:357, 1944.
9. Janes, R. M.: Multiple Cavernous Hemangiomas of the Lungs Successfully Treated by Local Resection of the Tumors, Brit. J. Surg. **31**:270, 1944.
10. Sisson, J. H., Murphy, G. E., and Newman, E. V.: Multiple Congenital Arteriovenous Aneurysms in the Pulmonary Circulation, Bull. Johns Hopkins Hosp. **76**:93, 1945.
11. Alexander, W. S.: Hemangioma of the Lung; Report of a Case Showing Polycythemia, New Zealand M. J. **44**:180, 1945.
12. Makler, P. T., and Zion, D.: Multiple Pulmonary Hemangiomas, Am. J. M. Sc. **211**:261, 1946.
13. Beierwaltes, W. H., and Byron, F. X.: Pulmonary Arteriovenous Aneurysm With Secondary Polycythemia, J. A. M. A. **134**:1069, 1947.
14. Burchell, H. B., and Clagett, O. T.: The Clinical Syndrome Associated With Pulmonary Arteriovenous Fistulas, Including a Case Report of a Surgical Case, AM. HEART J. **34**:151, 1947.
15. Watson, W. L.: Pulmonary Arteriovenous Aneurysm; A New Surgical Disease, Surgery **22**:919, 1947.
16. Bisgard, J. D.: Pulmonary Cavernous Hemangioma With Arteriovenous Fistula, Surgical Management. Case Report, Ann. Surg. **126**:964, 1947.
17. Abbott, M.: Atlas of Congenital Cardiac Disease, New York City, The American Heart Association, Inc., p. 60 (Series VIII).
18. White, P. D.: Heart Disease, ed. 3, New York City, 1944, The Macmillan Company.
19. Taussig, H. B.: Congenital Malformations of the Heart, New York City, 1947, The Commonwealth Fund.
20. Robb, G. P., and Steinberg, I.: A Practical Method of Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Veins in Man, J. Clin. Investigation **17**:507, 1938. See also: Am. J. Roentgenol. **41**:1, 1939; and J. A. M. A. **114**:474, 1940.

A CASE OF ANGINA PECTORIS PRECIPITATED CHIEFLY BY TOBACCO SMOKING AND MEALS

REPORT OF A CASE

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THE history of a patient with angina pectoris indicated that the attacks were brought about principally by eating and smoking. Since tobacco is an uncommon precipitating agent, and since the attacks were found to be accompanied by immediate reversible electrocardiographic changes, a detailed report of this particular case seemed justified.

CASE REPORT

In January, 1939, a 57-year-old typographer began to have chest pains, which rapidly became more severe. Initially, the attacks began with an oppressive pain across the back between the shoulders which radiated to the neck and both mandibles. He was occasionally subjected to spontaneous attacks at night. However, the seizures usually were attributable to one of the four classical reasons: cold, exertion, emotion, and heavy meals.

In the spring of 1944, the character and distribution of the pains changed. They were intensified, and shifted to the cardiac region, radiating from there toward the shoulders and the left lower jaw, and were often combined with a sensation of anguish. Otherwise, the patient seemed exceedingly neurolabile and frequently complained of diffuse dorsal and abdominal pains. These may have been associated with a duodenal lesion which was discovered later in his illness.

During the period of 1944 to 1946, he was given treatment at Sabbatsberg's Hospital on five separate occasions, and later in the Nylin Clinic at Södersjukhuset under the diagnosis of cardio-sclerosis with angina pectoris, chronic gastritis, and neurosis.

When the patient was studied in October and November, 1946, it was learned that he had been unable to work for four months. Although he was able to walk almost without pain at a slow pace, rapid walking and heavy meals, in particular, provoked anginal attacks. An electrocardiogram showed a heart rate of 75 beats per minute. The P-Q interval was 0.16 second and the QRS interval 0.08 second. The R deflection showed a notch in the descending limb. There was left axis deviation. All RS-T segments were normal, and all T waves were positive. Tracings made in the supine and erect postures brought out no findings of interest. (Earlier electrocardiograms had shown transient A-V block, minor changes in the T-wave positivity, and definite changes of the posterior thoracic lead, indicating a posterior coronary syndrome.)

Because of the patient's insistent statements regarding a connection between pain and meals, especially when the latter contained semiliquid food, the following test was performed by one of us (O. G.). After a meal suitably prepared for the occasion, tracings were obtained at frequent intervals. Significant changes were noted to coincide with the occurrence of the customary subjective symptoms. These changes consisted of pronounced depressions of the RS-T segment in Leads I and II, the development of a diphasic T wave in Lead I, and a change in the configuration of the QRS complex in Lead III. As the pains subsided, the electrocardiogram gradually resumed the configuration it had when the patient was at rest. Thus, the test disclosed a latent anterior coronary insufficiency, apart from the old posterior one diagnosed previously.

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Although the patient seemed to improve as a result of treatment and stated that he felt distinctly better, he found the hospital rules insupportable and was discharged (as on previous occasions) at his own request.

During the following winter and summer, he did surprisingly well and was able to work without too much inconvenience. He derived great help from nitroglycerin. Toward the fall of 1947, however, his troubles again rapidly increased. Anginal seizures of the same type as before made it increasingly difficult for him to get to work. He could now endure but slight exertion and was subjected to practically constant pains when exertion had been preceded by a meal.

When the patient was again studied in 1947, he related that he had noticed for a long time that his pains could be precipitated by tobacco smoking, and especially by the combination of smoking and exercise. When, a few years before, he had been able to walk around a block at a slow pace without any particular inconvenience, after smoking half a cigarette he was overcome half-way around the block by such severe pains that he could only return home with much difficulty after a long rest. The amount of tobacco required to precipitate an attack had gradually

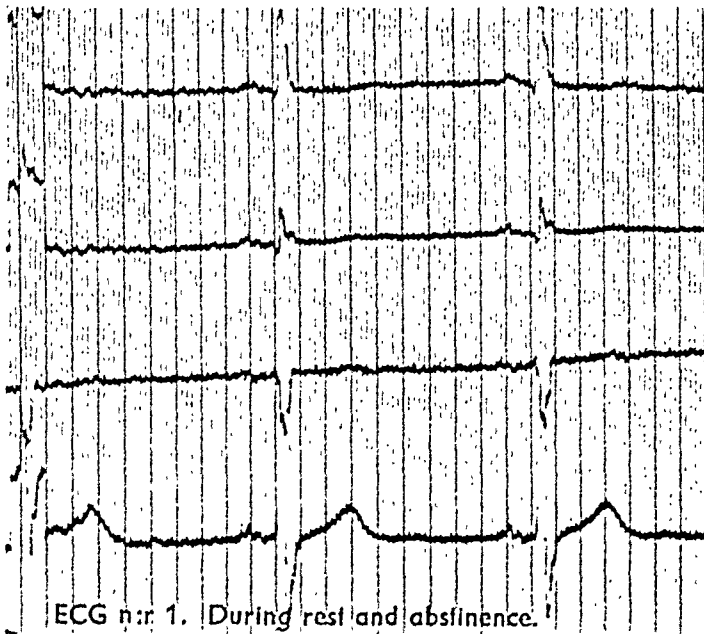


Fig. 1.

diminished. When our studies were made he was forced to smoke with great caution, since even one or two inhalations of smoke would cause serious inconvenience, although mere puffs without inhalation did not trouble him at all. In spite of the effects of smoking, he could not be prevailed upon to give up tobacco. When the patient himself was asked to evaluate the factors precipitating his attacks, he unconditionally put smoking first, meals second, and exercise third, the last one being the factor apparently most easily restricted.

Since in this particular case smoking was expected to accentuate the latent coronary insufficiency, one of us (B. v. A.) carried out a smoking test with electrocardiographic control on Nov. 3, 1947. The results follow.

With the patient recumbent after a rest, there were no symptoms. Blood pressure was 150/100. The control electrocardiogram (Fig. 1) showed a heart rate of 60 per minute, normal rhythm with a left axis deviation, P-Q intervals of 0.16 second, QRS duration of 0.08 second, normal RS-T segments, slightly flattened T waves in Leads II and III, and normal upright T waves in Lead IVF.

The patient then began to smoke a cigarette.

Clinical Observations.—

At 45 seconds moderate pain in both arms developed.

At 2 minutes the pain had increased and radiated to both jaws.

At 4 minutes the pain was accentuated.

At 5 minutes the blood pressure was 160/100.

At 6 minutes the pain began to subside.

At 8 minutes the pain was of no moment.

At 9 minutes the second cigarette was lighted.

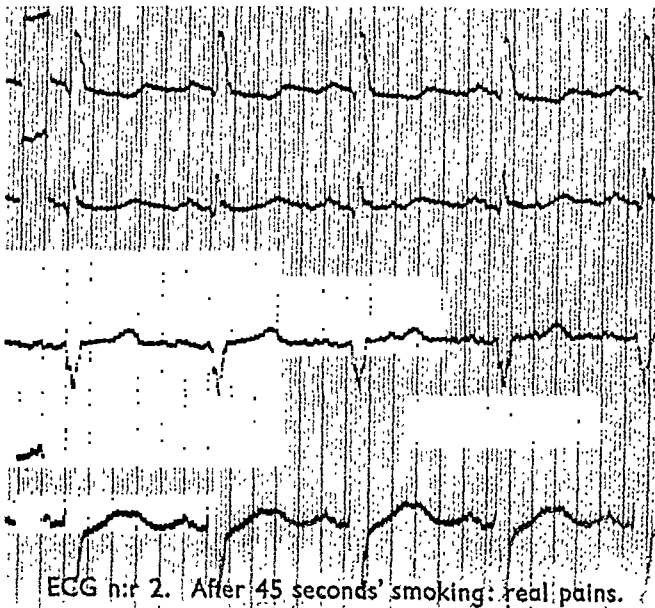
At 10½ minutes the blood pressure was 175/100.

At 12 minutes no subjective symptoms were present.

At 15 minutes the blood pressure was 150/90. The patient felt cold and looked very pale. He seemed intoxicated.

At 17 minutes the test was discontinued after inhalation of the smoke of one and one-half cigarettes.

At 19 minutes the blood pressure was 145/85. There were no subjective symptoms, but the patient looked pale and his skin was cool to touch.



ECG nr 2. After 45 seconds' smoking: real pains.

Fig. 2.

Electrocardiographic Observations.—

At 45 seconds after the beginning of the experiment (Fig. 2) the electrocardiogram showed a heart rate of 100 beats per minute, a normal rhythm, P-Q and QRS times unchanged, depression of the RS-T segment and downward displacement of the T wave of Lead I, upright T wave in Lead III, and flattening of the peak of the T wave in Lead IVF.

At 6 minutes (Fig. 3) the previously flattened T wave in Lead IVF became depressed and diphasic.

The anginal pain, felt as quickly as forty-five seconds after the smoking, disappeared after about ten minutes, as did the electrocardiographic changes. The record shows that the systolic blood pressure rose moderately in the initial stage, only to fall again later, while the diastolic pressure, which was initially constant, showed a later decrease.

A short while after the test, the patient took a few steps and was subjected to a severe anginal attack. This was quickly overcome by means of nitroglycerin and Oxyphyllin administered intravenously. He refused to stay at the hospital and set out for home. After walking for about fifteen minutes, he had a new attack, which was extremely violent. After resting for twenty

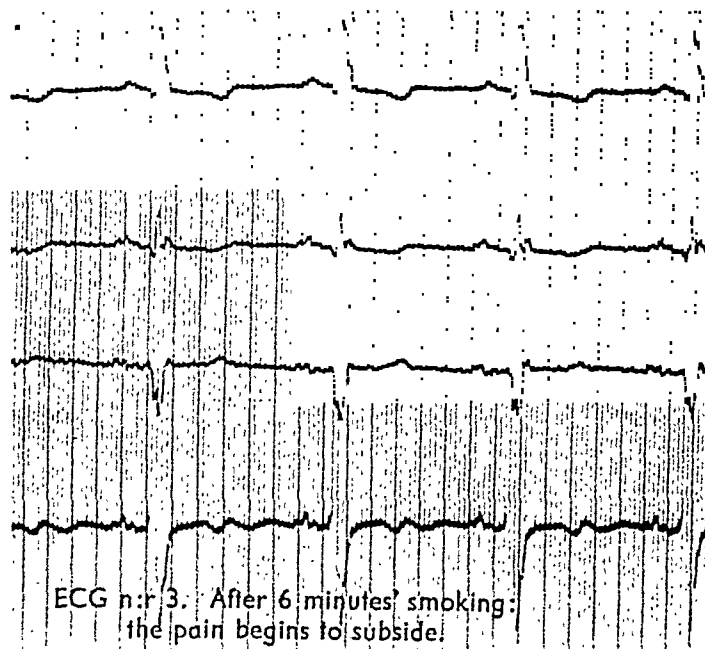


Fig. 3.

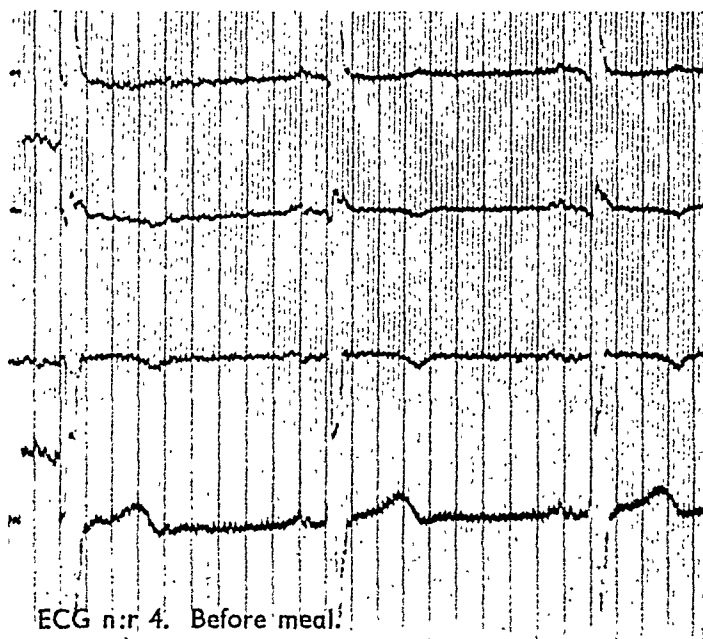


Fig. 4.

minutes, he was able to continue by car. However, because he lived on the fifth floor in a house without an elevator, he still had to submit to considerable exertion, with subsequent severe pains. After a light meal further deterioration occurred and he was brought back to the hospital in a severe anginal state which was eased only after energetic treatment.

During the physical examination at this admission, his manner was affected and he groaned aloud with pain. There were no symptoms of decompensation. The heart was clinically normal. The blood pressure was 150/100. The electrocardiogram showed the changes in the RS-T segments and T waves generally manifested during his attacks.

The following morning he ate a light meal consisting of porridge, milk, and three small sandwiches. After six minutes the expected attack set in and increased in intensity until twenty minutes had passed, when the attack was brought to an end by means of nitroglycerin. The same thing happened after he took a few puffs of a cigarette.

An electrocardiographic study was made during the attack induced by the meal just referred to. An electrocardiogram made before the meal (Fig. 4) was similar to previous control tracings except that the T wave was inverted in Lead II. The electrocardiogram made six minutes after the meal (Fig. 5) showed a depressed RS-T segment in Leads I and IVF, an inverted T wave in Lead I, and a diphasic T wave in Lead II.

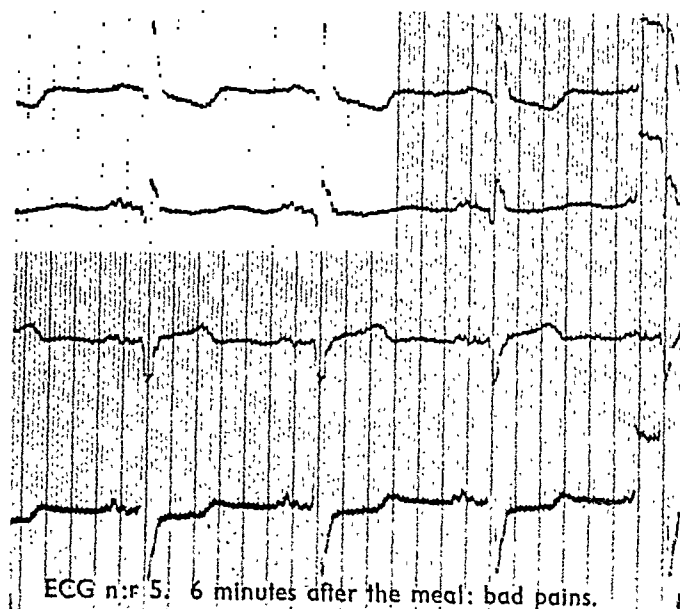


Fig. 5.

Following this electrocardiographic study, the patient remained in the hospital. During this period of observation it was found that the pulsations of the heart were rather small and that the volume of the heart was 910 c.c., which corresponds to 480 c.c. per square meter of body surface. No pulmonary congestion was present. Roentgenologic study of the stomach showed deformity of the duodenum.

DISCUSSION

We have been able to establish in this particular case that a meal as well as light tobacco smoking will precipitate distinct anginal attacks accompanied by definite but transient electrocardiographic changes. Heavy meals are assumed to cause anginal attacks as the result of dilatation of the stomach, which produces an increase in the minute volume of the circulation. This increase is stated to be capable of reaching a maximum of 30 to 40 per cent after one hour. A heavy meal is also thought to be able to set up reflexes which are capable of constricting the coronary vessels of predisposed persons. The combination of extra work and

a diminished blood supply to the heart furnishes a logical explanation for the anginal attacks which are occasionally precipitated by eating.

Tobacco smoking may also provoke angina pectoris, although this is by no means common. It is possible that the same mechanism operates in precipitating the less common instances of angina pectoris which are induced by smoking. This question will be discussed in some detail by V. Ahn in a later paper.

SUMMARY

A case of angina pectoris is described in which the attacks are chiefly precipitated by tobacco smoking and meals, as well as by the more usual precipitating factors.

Electrocardiograms showing reversible changes characteristic of temporary insufficiency of the coronary arteries, were recorded during an attack of angina pectoris induced by eating and during an attack induced by smoking.

MITRAL STENOSIS AND INSUFFICIENCY PRODUCED BY CARDIAC "MYXOMA"

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RARE as cardiac tumors are, it is surprising to discover in reviewing the literature how many have been reported. At present they remain largely a matter of academic interest, but with the recent great impetus in cardiac surgery, the possibility of surgical removal of the benign heart tumor does not now seem remote. The report of a case is offered in the hope that, as more cases are made public, a clinical picture may develop to facilitate the ante-mortem diagnosis.

CASE REPORT

Clinical History.—A 64-year-old doctor's wife entered the hospital (47-3484) with a two-year history of progressive weakness and a weight loss of thirty to thirty-five pounds. She had had intermittent episodes of night sweats, which had become more severe in the last two months. For two weeks prior to admission she had experienced chilly sensations, which usually occurred in the late afternoon and were followed by a low-grade fever. For two months previously there was epigastric distress described as an "emptiness in the pit of the stomach." This was not related to the ingestion of food, and occurred shortly after the patient arose in the morning and was relieved when she was lying down. The patient had visited several clinics, and except for cystitis, which had been diagnosed two years before and had disappeared on sulfonamide therapy, nothing had been found to explain her weakness and weight loss.

In the past history the patient had suffered from "infectious rheumatism" at the age of 16, and brucellosis at the age of 47.

Physical examination on admission revealed a woman apparently chronically ill and showing evidence of considerable weight loss. The temperature was 99, the pulse 84, and the respiratory rate 20. The positive findings were limited to the heart and abdomen. There was a diffuse precordial impulse, and the point of maximum intensity was in the fifth intercostal space, 2.0 cm. outside the midclavicular line. The rate was 84 and the rhythm regular. There was a soft pre-systolic and a harsh systolic murmur at the mitral area, and the second aortic sound was accentuated. The blood pressure was 90/60. The right kidney was easily palpable, not enlarged, and freely movable.

Urinalysis was negative except for 6 to 8 white cells. There were 12 Gm. of hemoglobin and the red count was 4.7 million. The white cells numbered 7.3 thousand, with 59 per cent neutrophils, 40 per cent lymphocytes, and 1 per cent eosinophiles. The Mazzini test for syphilis, and an agglutination test for brucellosis were negative. The stool culture was noninformative, and the blood culture was sterile. A complete x-ray examination of the gastrointestinal tract was said to be negative. An intravenous pyelogram showed a low-lying right kidney whose function, however, was good. An x-ray examination of the chest uncovered moderate cardiac enlargement with "mitralization" of the left border; the lung fields were clear.

During her eight-day hospital stay the patient occasionally had an afternoon rise of temperature, which never exceeded 100.4° Fahrenheit. Although she was ambulatory, she com-

plained of weakness. The clinical impression was that of rheumatic heart disease with mitral stenosis and insufficiency. No diagnosis was made to explain her leading symptoms.

One month later, the woman re-entered the hospital with complaints of dyspnea and a tickling sensation in the throat causing paroxysms of coughing. These symptoms were intensified when she lay on her back or left side, and were relieved when she lay on the right side. Her family physician stated that the patient had developed cardiac decompensation at home but had responded well to digitalis medication.

The temperature was 98, the pulse 80, the respiratory rate 20, and the blood pressure 80/50. The physical examination was essentially the same as on the previous admission.



Fig. 1.—Heart. Left atrium and ventricle incised to expose pedunculated "myxoma" extending into the ventricle from above the mitral ring area.

The urine showed a heavy trace of albumin, with 5 to 10 white cells. The hemoglobin was 12.0 grams; the red count, 4.1 million; and the white cells numbered 8.0 thousand, with 73 per cent neutrophils, 26 per cent lymphocytes and 1 per cent eosinophiles. The agglutination test for brucellosis was repeated, and now was positive in a dilution of 1:40. An electrocardiogram on the twentieth hospital day showed flat T waves in Leads I and IV, and inversion of the T waves in Leads II and III. The urea nitrogen was 59 mg., and a repetition of the intravenous pyelogram now revealed poor function of both kidneys, particularly of the right.

The patient's condition remained relatively unchanged until the seventeenth hospital day, when she began to develop edema of the lower extremities, râles at the lung bases, and a palpable

liver, in spite of treatment with digitalis and diuretics. The next day she suffered a sudden attack of syncope, from which she recovered within a few minutes. On the thirty-seventh day she complained of severe pain in the left leg, which was noted to be cold, mottled, and pulseless. Heparin administration was begun immediately, but the patient continued to sink rapidly and died in obvious heart failure thirty-nine days after having been admitted to the hospital for the second time.

Necropsy.—A post-mortem examination (47-A-063) was done two hours after death, and the findings were chiefly related to the heart. That organ weighed 375 grams and measured 16 cm. in the greatest transverse diameter. The tricuspid ring was 11.5 cm. in circumference and the leaflets were slightly thickened at their free edges; the cords appeared natural. The pulmonic valve was 8.0 cm. in circumference. In the smaller branches of the pulmonary artery were numerous small emboli, well-adherent to the arterial wall.

The left atrium was dilated, and attached to and extending from its endocardium above the posterior commissure of the mitral valve was a polypoid mass, 6.0 by 5.0 by 3.0 cm. (Fig. 1.)

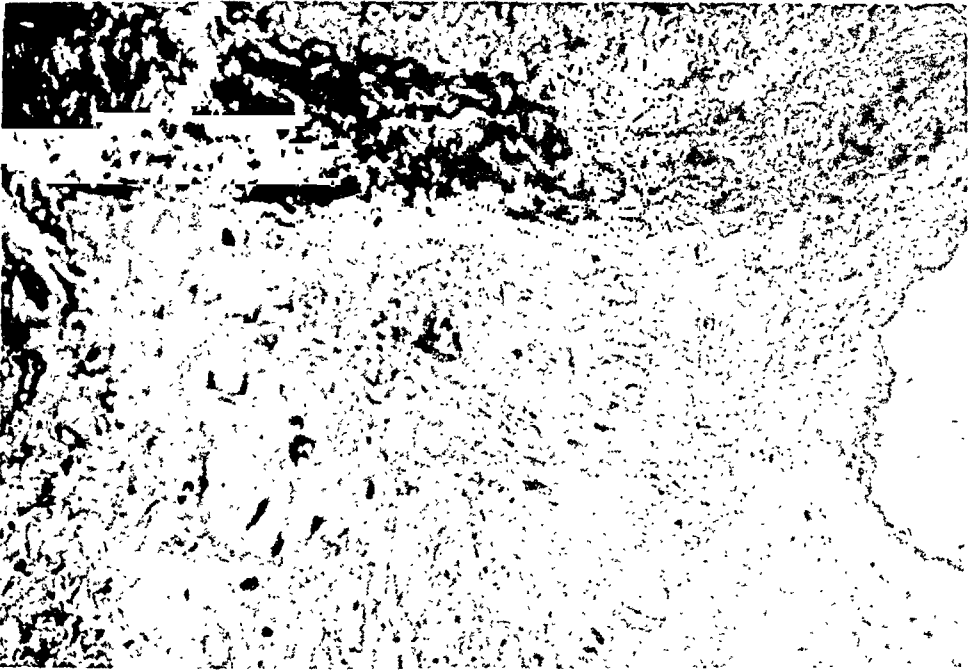


Fig. 2.—Heart. Photomicrograph of junction of atrial wall (horizontal, broad, dark area, above), and base of "myxoma." The clear spaces with small, deep-staining nuclei are identified as myxoid cells.

This reached into the left ventricle to within 3.0 cm. of the apex. The base of the tumor was 1.5 cm. wide.

There was an embolus in the left femoral artery and a thrombus in the accompanying vein directly adjacent to the artery. This was the cause of the incipient gangrene of the lower limb.

Microscopically, the cardiac tumor was largely formed of relatively immature mesenchymal elements. Centrally, there were large areas of thrombus. Adjacent to the latter there was granulation tissue in which were large mononuclear cells laden with hemosiderin. In the base of the mass the loose tissues were filled with an indefinitely outlined basophilic material similar to that seen in myxoid tissues. Some cells closer to the base were surrounded by large spaces with a thin rim of basophilic material. Lying within the spaces were single, round-to-oval eosinophilic refractile masses containing one to eight small, round, relatively solid nuclei (Fig. 2). There was scarring of the inner portion of the atrial muscle adjacent to the attachment of the tumor. At the center of the base of the mass was a small artery continuing into the endocardium.

DISCUSSION

Much discussion has centered about the question of whether the type of tumor discussed here originates from primitive mesenchyme or whether it is formed from the organization of a thrombus. Among the authors who believe that these tumors are true neoplasms and arise from mesenchymal tissue are Ewing,² Yater,³ Strauss,⁴ Ribbert,⁵ and Brown.⁶ Ribbert maintains that rests of embryonal mucoid tissue may persist in the heart, generally near the rim of the fossa ovalis, the most frequent site of origin of the myxoma. In refuting the thrombus theory, Brown states that organization of thrombi occurs most often in the peripheral vessels and in the ventricles; they are rarely the site of myxomas. He also points out that the occurrence of myxomas in otherwise normal hearts favors the neoplastic theory.

The proponents of the thrombus theory include Thorel,⁷ Warthin,⁸ Jaleski,⁹ Maun,¹⁰ and Anderson and Dmytryk.¹¹ In reporting his case, Maun presented several reasons why the tumor is of thrombotic origin and not a true myxoma. The chief features were the presence of injury to the auricular wall at the site of attachment of the pedicle, and the histologic picture of a thrombus which failed to show the microscopic picture of a myxoma or to stain for mucin.

In a recent extensive monograph, Mahaim¹² straddles the dilemma by speaking of "myxomatous polyps."

In our case, the finding of myxomatous elements near the base of the tumor surrounded by thrombotic material suggests a true primary neoplasm on which there has been superimposed thrombus formation.

Yater³ quoted Mandelstamm,¹³ who collected 143 cases of primary tumors of the heart. The greater number of these, 117, were benign, and were chiefly myxomas. There were, however, twenty-six which were malignant, mostly sarcomas. In the 214 cases assembled by Yater, the myxomas led in frequency, with seventy-five of that type. There were twenty-five tumors classed as fibromas, forty-six as sarcomas, forty-one as rhabdomyomas, and twenty-one as lipomas. The six others included instances of lymphangio-endothelioma, hemangio-endothelioma, leiomyoma, and rhabdomyosarcoma. Lymburner,¹⁴ quoted by Barnes, Beaver, and Snell¹⁵ in 1934, found 226 cases of primary tumors of the heart in the literature. He added four cases of his own, collected from 8,550 post-mortem examinations at the Mayo Clinic. Of interest is the fact that there were fifty-two cases of metastatic tumors of the heart in the same series of necropsies.

The symptomatology of cardiac tumors is extremely variable, and depends on the type of tumor, size, and location. While there are no symptoms which are characteristic, certain abnormalities should make the examining physician suspicious of their presence. Abnormalities of cardiac rhythm, particularly variable degrees of heart block, sudden onset of congestive heart failure in the absence of previous heart disease, or bloody pericardial effusion should suggest the presence of a neoplastic cardiac process.¹⁶ In any individual with a known malignant tumor, the appearance of any of these symptoms or signs tends to implicate metastasis to the heart. In 1942 Doane and Pressman¹⁷ reviewed nine-

teen cases of metastatic cardiac tumors that had been diagnosed before death and added one of their own. Among these twenty cases the right auricle was the site of metastasis in nine instances. These workers emphasize that whenever the right side of the heart is involved, there is great likelihood that the interventricular septum will also be attacked by the same process, thus embarrassing the conduction system.

A primary malignant tumor of the heart should be considered whenever the signs already described are present, and if other causes for such cardiac dysfunction can reasonably be ruled out. There are only two reports of primary malignant cardiac tumor diagnosed ante mortem. The case of Barnes, Beaver, and Snell¹⁵ was uncovered by the coexistence of signs of acute pericarditis, the sudden appearance of heart block, and the presence of metastasis to the muscles of the shoulder girdle. Shelburne's case¹⁸ was diagnosed before death from the rapid accumulation of bloody pericardial effusion, after all other causes for this condition had been excluded.

Credit for the only ante-mortem diagnosis of a primary benign heart tumor usually is given to Pavalowsky, in 1893.²³ However, this has been challenged by Strauss⁴ and others.

The most common benign cardiac tumor is the myxoma, which arises most frequently in the left auricle in the region of the fossa ovalis. It often attains large size, and, because of its location and pedunculated character, produces symptoms most commonly diagnosed as mitral valvular disease.¹⁹⁻²³ In 1941, Lisa, Hirschhorn, and Hart²⁴ reviewed seventy-two cases of primary cardiac tumors already reported in the literature. More than half the benign tumors were myxomas, and, in turn, in more than half of these an ante-mortem diagnosis of mitral stenosis was made. This is in contrast to the single instance of a diagnosis of mitral stenosis in the group of primary malignant heart neoplasms. Several cases of myxomas have been reported with the ante-mortem diagnosis of subacute bacterial endocarditis, because of the mitral murmur and embolic phenomena.⁶ In our case, the diagnosis of rheumatic heart disease with mitral stenosis and insufficiency was made, and subacute bacterial endocarditis was thought of because of the persistence of low-grade fever.

How these cases can be differentiated from true mitral valvular disease still remains a problem. An awareness of these tumors, despite their rarity, is still the best clinical tool. Yater,³ among others, maintains that a negative rheumatic history is helpful. This may be of little value since it is well known that an established endocarditis may exist without any history of an acute attack. Of greater value are the following: (1) modification of the character of the apical murmur with change of bodily position of the patient; (2) sudden attacks of syncope, dyspnea, or cyanosis on change of position; (3) abnormalities of the x-ray cardiac silhouette,²⁶ particularly rapid increase in size of the right side of the heart; (4) rapid onset of progressive heart failure in a patient with no known cardiac disease who does not respond well to digitalis; and (5) sudden appearance of cardiac murmurs in a patient who has been under medical supervision and in whom no murmurs have been noted previously.

It is well, therefore, to remember that cardiac tumors exist, and their presence should be suspected in those patients with mitral stenosis which does not behave in typical fashion. It is possible that, as the demand for a more positive method of diagnosing cardiac tumors increases, a laboratory technique will be devised to fulfill the need. Although angiocardiology has not been reported to have been used for visualization of these lesions, it may prove to be an additional implement in the armamentarium for the diagnosis of cardiac tumors.²⁷

SUMMARY

A case of a myxoma of the left auricle, diagnosed ante mortem as rheumatic heart disease with mitral stenosis and insufficiency, is reported.

Autopsy findings are presented, with a brief discussion as to the character of these tumors.

A review of the literature on incidence and frequency of cardiac tumors is given.

Symptomatology of cardiac tumors is discussed, with special reference to those features aiding in the ante-mortem diagnosis of the most common benign type, the myxoma.

We are indebted to Dr. N. L. Salon for furnishing the clinical history, and to Mrs. Grace Brooks for technical assistance.

REFERENCES

1. Beck, C. S.: Intrapericardial Teratoma and Tumor of Heart: Both Removed Operatively, *Ann. Surg.* **116**:161, 1942.
2. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, 1940, W. B. Saunders Company, pp. 187-188.
3. Yater, W. M.: Tumors of Heart and Pericardium; Pathology, Symptomology, and Report of Nine Cases, *Arch. Int. Med.* **48**:627, 1931.
4. Strauss, S.: Primary Benign Tumors of Heart, *Arch. Int. Med.* **62**:401, 1938.
5. Ribbert, M. W. H.: *Geschwulstlehre für Aerzte und Studierende* (cited by Ravid and Sachs²⁵).
6. Brown, W. O.: Myxoma of Heart, *AM. HEART J.* **31**:373, 1946.
7. Thorel, C. h.: Pathologie der Kreislauforgane, *Ergebn. d. allg. Path. u. path. Anat.* **9**:901, 1903 (cited by Brown⁶).
8. Warthin, A. S.: Myxoma-like Growths in the Heart, Due to Localization of *Spirochaeta Pallida*, *J. Infect. Dis.* **19**:138, 1916.
9. Jaleski, T. C.: Myxoma of Heart Valves, *Am. J. Path.* **10**:399, 1934.
10. Maun, M. E.: Polypoid Thrombus of Left Auricle With Report of Case, *AM. HEART J.* **26**:549, 1943.
11. Anderson, W. A. D., and Dmytryk, E. T.: Primary Tumor of the Heart Containing Epithelium-like Elements, *Am. J. Path.* **22**:337, 1946.
12. Mahaim, I.: *Les Tumeurs et les polypes du coeur*, Paris, 1945, Masson, pp. 113-151.
13. Mandelstamm, M.: Ueber primäre Neubildungen des Herzens, *Virchows Arch. f. path. Anat.* **215**:43, 1923 (cited by Yater³).
14. Lymburner, R. M.: Tumors of the Heart; Histopathologic and Clinical Study, *Canad. M. A. J.* **30**:368, 1934.
15. Barnes, A. R., Beaver, D. C., and Snell, A. M.: Primary Sarcoma of Heart, *AM. HEART J.* **9**:480, 1934.
16. Tedeschi, C.: Primary Sarcoma of Heart, *Arch. Path.* **37**:70, 1944.
17. Doane, J. C., and Pressman, R.: Antemortem Diagnosis of Tumors of Heart, *Am. J. M. Sc.* **203**:520, 1942.
18. Shelburne, S. A.: Primary Tumor of Heart, With Special Reference to Certain Features Which Led to Logical and Correct Diagnosis Before Death, *Ann. Int. Med.* **9**:340, 1935.
19. Field, M. H., Donovan, M. A., and Simon, H.: Primary Tumor of Left Auricle Simulating Mitral Stenosis, *AM. HEART J.* **30**:230, 1945.

20. Hamilton-Patterson, J. L., and Castleden, L. I. M.: Intra-cardiac Tumors, *Brit. Heart J.* 55:103, 1942.
21. Dexter, R., and Work, J. L.: Myxoma of Heart, *Arch. Path.* 92:995, 1941.
22. Haugh, G. H., and Bennett, G. A.: Polypoid Fibroma of Left Auricle (So-called Cardiac Myxoma) Causing Ball-Valve Action, *AM. HEART J.* 5:787, 1929.
23. Hoffman, P. D.: Tumor of Left Auricle, *Proc. New York Path. Soc.* 21:85, 1921.
24. Lisa, J. R., Hirschhorn, L., and Hart, C. A.: Tumors of Heart, *Arch. Int. Med.* 67:91, 1941.
25. Ravid, J. M., and Sachs, J.: Tumors of Heart, *AM. HEART J.* 26:385, 1943.
26. Bennett, D. W., Konigsberg, J., and Dublin, W.: Primary Tumor of Heart Producing Unusual Cardiac Shadow in Roentgenogram, *AM. HEART J.* 16:117, 1938.
27. Dock, W., and Snapper, I.: *Recent Advances in Internal Medicine*, New York, 1947, Interscience Publishers, Inc., pp. 113-151.

BRUCELLA MELITENSIS ENDOCARDITIS

REPORT OF A CASE

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THE occurrence of endocarditis as a complication of *Brucella* infection is rare. A review of the literature by DeGowin and associates¹ in 1945 revealed only sixteen cases, one of which was caused by *Br. suis*, and the others by either *Br. abortus* or *Br. melitensis*. Since that time only one additional case has been reported,² bringing the total number of cases to seventeen. Call and associates³ noted that in all reported cases except four there was either historical or pathologic evidence of previous rheumatic fever. The infection occurred on a congenital bicuspid aortic valve in one case and on apparently normal valves in only two instances. The case to be reported, although it does not fulfill completely the rigid specifications of Spink and Nelson,⁴ since the post-mortem cultures from the involved valve were contaminated, is felt, by virtue of the positive blood cultures for *Br. melitensis* and a demonstrated vegetation, to qualify as another example of endocarditis caused by *Brucella* organisms.

CASE REPORT

The patient, a 31-year-old white man, was admitted to the Albany Hospital on July 18, 1943, with the chief complaint of malaise, fever, and dizziness of one week's duration. At the age of 11 years the patient was placed in bed for six months for an attack of acute rheumatic fever. He had been without complaints since then except for occasional attacks of palpitation. Five months prior to the present illness, the patient experienced pain in the precordium. He was digitalized by his local physician, and returned to work in ten days. Three weeks prior to admission, he noted the onset of weakness and fatigue, with diaphoresis. One week prior to admission he complained of malaise, aching bones, fever, and dizziness. Four days before admission he noted migrating pain in both ankles and feet. There was an eighteen-pound weight loss in the three weeks prior to admission.

The past history, family history, and systemic review were noncontributory, except that the patient had been reared on a farm.

On physical examination his temperature was 100° F., his pulse 80, his respiratory rate 22, and his blood pressure 170/90. The head and neck were normal. The heart was enlarged to the left and had a normal sinus rhythm. At the apex a systolic murmur and a rumbling presystolic murmur were heard, with accentuation of the mitral first sound. At the aortic area a rough systolic murmur and a blowing diastolic murmur were heard. Except for moderate tenderness in the metatarsal joints, there were no unusual physical findings. No petechiae were noted.

Significant laboratory findings included 40 red cells in the urine sediment. Three blood cultures were negative. The Wassermann test was negative.

The patient was discharged after twenty-four hours, against the advice of his physician, with a tentative diagnosis of rheumatic heart disease and subacute bacterial endocarditis, with focal embolic nephritis.

The patient was next seen eight months later, in March, 1944. Four months prior to admission he had been troubled by occasional diarrhea, with cramps, and had had daily elevations of temperature ranging from 99° to 103° Fahrenheit. There were no further complaints of arthritis or arthralgia. On physical examination the temperature was 102°, the pulse 120, the respirations 25, and the blood pressure 140/50. The physical findings were approximately the same as on the previous admission, except for an increase in the intensity of the sounds heard at the aortic area and moderate tenderness in both upper abdominal quadrants. Again no petechiae were noted.

No red cells were found in the urine on this admission. Agglutination tests for typhoid, paratyphoid, and Proteus OX 19 were negative. Blood cultures and stool cultures were negative. On admission, *Br. abortus* was agglutinated in a titer of 1:40, and four days later at 1:80.

The patient's temperature fell to normal gradually and he was discharged five days after admission.

The patient's third admission took place two weeks later. His complaints were of continued fever, chest pain, and discomfort in the shoulder joints. There had been frequent episodes of epistaxis.

On physical examination the temperature was 99.4° F., the pulse 120, the respirations 32, and the blood pressure 130/70. At this time it was thought that a pericardial friction rub was heard, and that the spleen was slightly enlarged. There had been no other significant change since the previous admission.

The electrocardiogram on admission was normal. A microcytic anemia and an elevated sedimentation rate were present. Blood cultures taken on admission and three, four, five, and seven weeks thereafter were negative. However, two blood cultures taken on successive days one month after admission were positive for *Br. melitensis*, as was one culture taken six weeks after admission. Three weeks after admission *Br. melitensis* was agglutinated in a titer of 1:160. At all times the white cell count and urine were normal.

Clinically, the patient's course was progressively downhill. Daily temperature elevations occurred. The patient was digitalized. The spleen gradually grew larger, conjunctival petechiae appeared, and the fingers became clubbed. The diastolic murmur at the aortic area increased in intensity. One month after admission the patient had a three-day episode of generalized arthralgia, which responded to salicylates. Since penicillin was not available, only supportive therapy and blood transfusions were utilized. The patient died in May, 1944, approximately two months after his final admission.

Necropsy.—Chronic passive congestion of all viscera was noted, but specific pathologic change was seen only in the heart.

The heart was enlarged, weighing 690 grams, and all its chambers, especially the left ventricle, were dilated. The epicardial surfaces were covered with a thin layer of fibrinous exudate, evidence of acute pericarditis. The coronary arteries and their branches were not enlarged or inflamed, and their walls were thin and pliable.

When the heart was sectioned, the left ventricular myocardium was found to be dull beefy-red in color, soft and flabby in consistency, and markedly hypertrophied, measuring from 1.8 to 2.0 cm. in thickness. The right ventricular myocardium was not remarkable. The mural endocardium was generally smooth and glistening, and the tricuspid, pulmonic, and mitral valves were thin, delicate, and pliable.

The aortic valve showed marked pathologic changes. The anterior or middle cusp of this valve was almost completely hidden beneath a large, irregularly ovoid, friable vegetation, the surface of which was covered by a thin layer of freshly clotted blood. The right and left posterior cusps were contracted and shortened and their surfaces were nodular as a result of replacement by dense, old, fibrous tissue. At their edges they blended into the large, friable, fibrinous vegetation on the anterior cusp. From these old sclerotic changes it is obvious that the aortic valve was the site of a diffuse inflammatory process at some previous time; it seems probable that the inflammatory process was rheumatic in character.

Careful inspection of the anterior cusp with the large, fresh vegetation showed that this structure was also thickened and sclerosed, as was the aortic ring, which was markedly narrowed, measuring only 6.0 cm. in circumference. Beneath the vegetation itself the cusp was ulcerated and in one place actually perforated.

The aortic valve was, therefore, the seat of two pathologic processes: one, an old, healed inflammatory lesion, presumably rheumatic, with fibrosis and shortening of the cusps, and resulting stenosis; the other, a recent superimposed acute active infectious process, with ulceration and perforation of the anterior cusp and the formation of a large, fibrinous vegetation or thrombus over the affected cusp.

Histologic examination of the aortic cusps and the aortic ring showed evidence of an old, healed inflammatory process, with much fibrosis, especially of the cusps themselves. In addition, the anterior cusp was the seat of a superimposed acute suppurative inflammatory process, with ulceration and acute thrombus formation. This lesion was unquestionably infectious in nature.

Sections from the inflamed and ulcerated anterior cusp showed the large, friable vegetation observed grossly. The vegetation was a typical recent thrombus, being composed of masses of agglutinated platelets intermeshed with strands of fibrin and infiltrated with large numbers of neutrophils.

Sections stained by the classical Gram-Weigert method failed to disclose the presence of bacteria in the thrombus. However, since the microorganisms isolated from the heart's blood at autopsy, *Br. melitensis*, were gram-negative bacilli, the same sections from the thrombosed cusp were restained by the Gram-Weigert method but were not decolorized. These sections showed innumerable minute, short, well-stained coccobacilli which were distributed throughout many portions of the thrombus. They were present either singly or in small and large groups or clumps. Their morphology was typical of *Brucella* and the fact that they lost their deep purple stain when the Gram-Weigert preparations were decolorized definitely indicated that they were actually gram-negative bacilli.

In order to check these findings by another method designed to stain bacteria in tissues, the same sections were stained by McCallum's modification of Goodpasture's method for the demonstration of both gram-positive and gram-negative bacteria in tissues. In these preparations, careful examination disclosed the presence of the same minute, short coccobacilli which morphologically resembled *Br. melitensis*. As in the other preparations, they were present chiefly in small groups or clusters. In these preparations, however, they took the red stain, which, in this technique, indicates specifically their gram-negative character.

The finding, deeply embedded in the thrombus, of great numbers of minute, short, coccobacilli proved quite conclusively their etiological relation to the acute ulcerative valvulitis of the affected aortic cusp. The morphologic resemblance of these microorganisms to *Br. abortus*, the bacterium isolated from the heart's blood taken at necropsy, together with their proved gram-negative character, indicates that they are undoubtedly members of the genus *Brucella*, thus rounding out the evidence pointing to a member of this group of bacteria as the incitant of the ulcerative valvular infection. The dense sclerotic process which also involved this aortic cusp, as well as the other cusps, which were not acutely inflamed, is believed to be the result of a much more remote infection, which was probably rheumatic.

Post-mortem culture of the heart's blood revealed *Br. melitensis*. Culture of the lesion on the aortic valve was contaminated by diphtheroids, *Br. coli*, *Br. fecalis*, and *Br. alcaligenes*. The only other findings of interest noted on microscopic examination were small areas of focal glomerulonephritis.

COMMENT

It is probable that the patient had been suffering from brucellosis for at least one year prior to his death. One can speculate that the prolonged insult to the aortic valve, already the site of rheumatic alterations, led to the eventual development of the endocarditis.

It is of interest to note that in this case, as in many of those reported by Call and associates,³ the aortic valve was affected and an ulceration was present.

SUMMARY

A case of endocarditis, affecting a previously damaged aortic valve, occurring during a chronic infection due to *Br. abortus*, and associated with positive blood cultures for this organism, is reported.

REFERENCES

1. DeGowin, E. L., Carter, J. R., and Borts, I. H.: A Case of Infection With *Brucella Suis*, Causing Endocarditis and Nephritis: Death From Rupture of Mycotic Aneurysm, *AM. HEART J.* 30:77, 1945.
2. Quintin, T. J., and Stalker, M. R.: Endocarditis Due to *Brucella Abortus*, *Canad. M. A. J.* 55:50, 1946.
3. Call, J. D., Baggenstoss, A. H., and Merritt, W. A.: Endocarditis Due to *Brucella*: Report of Two Cases, *Am. J. Clin. Path.* 14:508, 1944.
4. Spink, W. W., and Nelson, A. A.: *Brucella* Endocarditis, *Ann. Int. Med.* 13:721, 1939.

Announcement

The American Heart Journal will be continued uninterruptedly as an independent monthly Journal under the editorial direction of leading cardiologists. It will not be the official organ of the American Heart Association after December, 1949.

The new Editor and Editorial Board will be announced in the December or the January issue.

Abstracts and Reviews

Selected Abstracts

Grossi, L., and Seitun, F.: Acquired Coarctation of the Aorta Near the Diaphragm. *Cuore e circolaz.* 32:271 (Oct.), 1948.

The authors describe a case of acquired coarctation of the descending aorta in a patient affected by diffuse scleroderma. The coarctation was related to sclerodermic retraction of the diaphragm with diminution of the hiatus and constriction of both the aorta and the esophagus. Confirmation of the diagnosis was obtained by means of tomographic studies.

LUISADA.

Jones, S. H., Younghusband, O. Z., and Evans, J. A.: Human Parabiologic Pygopagus Twins With Hypertension: Report of a Case With Clinical, Psychologic, and Endocrinologic Observations. *J. A. M. A.* 138:642 (Oct. 30), 1948.

This report relates the observations of the authors on a pygopagus, a set of twins conjoined at the buttocks. The fusion of the twins, Margaret and Mary, 34 years of age, resulted from fusion of anomalous sacral bones and of their perineum. A common anal orifice and rectum were present, with separate sigmoid colons. There were separate urethrae, vaginae and uteri, but the medial labiae were absent.

Margaret was thin and apprehensive, whereas Mary was stout and placid. Margaret had a Grade 2 hypertension, first discovered five months previously, and a systolic apical murmur was noted. She had also a leiomyoma of the uterus. She had had unilateral renal calculi at the age of 21 and had later been found to have a cystitis and urethral narrowing, for which dilatation had been performed. Mary had a mild labile hypertension which was normal at rest. Their mother had a marked hypertension.

The blood pressures of both twins showed generally parallel changes during their hospital course, Margaret's pressures being higher. The intravenous administration of tetraethylammonium chloride ("etamon chloride") to each of the sisters brought about a drop in the systolic and diastolic pressures of both, but the effect on Margaret's pressure was greater than that on Mary's even when the drug was administered only to Mary. This is indicative of increased vasomotor tone of the more hypertensive sister. The cold pressor test elicited rises in tension in each sister, but no crossed effect was noted; this is to be expected because vasomotor rather than chemical changes are involved in the cold pressor reaction. The sodium amytal and Mecholyl tests brought about significant pressure decreases in each sister individually; the lack of crossed effects with these procedures is apparently explained by the rapid removal of the drugs from the blood stream so that little or none reached the other sister. The urea clearance and phenolsulfonphthalein tests revealed evidences of renal damage in the more hypertensive twin; small amounts of phenolsulfonphthalein were found in the urine of the second sister even when the dye was administered to the other. After Iodopyracet injection was given intravenously to Margaret, her renal calices were not visualized by x-ray study and her bladder showed only poor concentration of the dye, whereas good visualization of Mary's urinary tract resulted; after administration of the dye to Mary, good visualization of Margaret's bladder was found.

The differences in the emotional make-up of the twins would indicate that emotional states are not mediated by way of the circulation. Although the parallelism of the blood pressure curves of the sisters suggests a humoral factor, this may have been due to similar responses to

environmental influences. Renal and tensional factors appeared to be of importance in the pathogenesis of Margaret's hypertension, while hereditary and humoral factors were apparently involved in the development of Mary's milder hypertension.

HANNO.

Blalock, A.: Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis. Surg., Gynec. & Obst. 87:385 (Oct.), 1948.

At the present time, there are only three general types of congenital cardiovascular defects which are amenable to surgical treatment: (1) patent ductus arterious, (2) coarctation of the aorta, and (3) an abnormality in which there is an inadequate pulmonary blood flow and in which mixed venous blood enters the arterial circulation.

The most frequently encountered condition of this third type is the tetralogy of Fallot. The severity of the cyanosis depends, in addition to other conditions, upon the degree of pulmonic stenosis and the degree of overriding of the aorta. The primary indication for the operation is an inadequate flow of blood to the lungs and an interventricular defect with an overriding aorta. The author performs the following anastomoses between the systemic and pulmonary arteries: (1) the proximal end of the right or left subclavian artery and the side of the right or left pulmonary artery, (2) the proximal end of the right or left subclavian artery and the distal end of the right or left pulmonary artery, (3) the proximal end of the carotid or innominate artery and the side or distal end of the right or left pulmonary artery, and (4) the side of the aorta and the side of one of the pulmonary arteries. The author prefers an anastomosis between the proximal end of the subclavian branch of the innominate artery and the side of one of the pulmonary arteries because the subclavian branch of the innominate artery when transposed makes a much more satisfactory angle with its parent vessel than is present when the subclavian branch of the aorta is used. The principle underlying all of the operative procedures is by-passing the point of stenosis in the pulmonary artery and allowing poorly oxygenated blood in the aorta to pass through the lungs. One should know preoperatively the position of the aorta, for this is of importance in determining the side on which the operation is performed. If the aorta descends on the right, and one wishes to use the subclavian branch of the innominate artery, the incision is made on the left. If the aorta descends on the right and one wishes to use the aorta, obviously the incision is made on the right.

The author presents several reasons why surgery should not be performed upon infants under the age of 2 years and he also gives an account of some of the anomalies of the blood vessels as observed in the course of operating. The mortality rate in patients 2 years of age and older with a typical tetralogy of Fallot is low. The danger is considerably greater when patients have associated complications such as rotation of the heart and cardiac arrhythmias. The majority of the patients who have survived the operative procedure are improved. The degree of improvement ranges from no limitations in activity to definite restrictions.

The author's series now totals 610 patients. There have been 108 deaths, an over-all mortality rate of 17.7 per cent. Twenty-seven of the deaths occurred during the operation, sixty-eight in the postoperative period and thirteen after discharge from the hospital.

BECK.

Smith, R. G., and Campbell, D. A.: Some Technical Considerations in the Arteriographic Examination of the Lower Extremity. Surgery, 24:655 (Oct.), 1948.

The authors describe the technique they found most effective in the study of the state of the arterial tree in the lower extremity by means of arteriography. The patient is placed on a mattress on the floor in order to obtain exposures at six feet with the ordinary radiographic equipment. This is not possible if the subject lies on the table. Exposures of this distance are needed to visualize the entire arterial tree of the lower extremity with one injection. The site of injection over the femoral artery is anesthetized with 2 per cent procaine, and 30 c.c. of 35 per cent Diodrast are injected into the artery through a long 18-gauge, short-beveled needle. Previously the proximal portion of the artery is compressed against the pubic ramus. When 25 c.c. have been injected,

the first exposure is made. Digital pressure on the artery is then released for four seconds, the remaining 5.0 c.c. of solution are injected, and the second exposure is made.

ABRAMSON.

Morrison, M., Richter, I. H., and Loewe, L.: Increased Platelet Clumping in Thromboembolic Disease. *Am. J. Clin. Path.* 18:879 (Nov.), 1948.

The authors studied routine differential blood films made on glass slides. The presence of blood platelet clumps and the number of platelets per clump were noted. Fewer than ten platelets per clump was considered normal; more than ten, abnormal.

In 100 control subjects, clumping was normal in 92 per cent and increased or abnormal in 8 per cent. Of 100 patients with various types of thromboembolic disease, clumping was normal in 19 per cent and increased in 81 per cent.

A correlation was attempted between increased platelet clumping and (1) thrombocytosis and megakaryocytosis, (2) increased erythrocyte sedimentation rate, (3) leucocytosis, and (4) fever. The authors felt that while thrombocytosis is usually associated with an increased tendency to clumping of platelets, such a tendency is not necessarily associated with, or caused by, thrombocytosis. A study of sternal bone marrow in fifty-one consecutive unselected patients was interpreted to indicate that megakaryocytosis parallels thrombocytosis in its relationship to clumping tendency. It was further found that while clumping is frequently associated with leucocytosis and/or increased sedimentation rate and sometimes with fever, this correlation is not consistent.

Because of the large number of patients in the thromboembolic group with increased clumping in contrast to the small number found in the control group, the authors conclude that this simple method of grading the tendency of blood platelets to clump may be of value in indicating a tendency of certain persons to develop thrombosis and may make it possible for these persons to be protected by the use of anticoagulants.

BEIZER.

Evans, L. R., and White, P. D.: Massive Hypertrophy of the Heart With Special Reference to Bernheim's Syndrome. *Am. J. M. Sc.* 216:485 (Nov.), 1948.

The study of thirty-three hearts weighing more than 750 grams showed that hypertensive heart disease was the etiological agent in sixteen, while rheumatic heart disease with mitral stenosis alone, or with aortic valve involvement, was responsible for eight and for the largest of the hearts examined. In the remainder the causes of enlargement were: calcareous aortic stenosis in three, and, in one each, hypertension and rheumatic heart disease, coronary arteriosclerosis, arteriosclerosis of the aorta with aneurysm, syphilitic aortitis with aortic regurgitation, Ayerza's disease, and chronic myocarditis.

In the hearts of the group with left ventricular hypertrophy (twenty-two patients), no instance could be found of isolated early signs or symptoms of right-sided failure. The authors have concluded from this analysis and from prior experience that they have yet to encounter any unquestionable case of so-called Bernheim's syndrome. It would appear sensible to drop this designation unless proof can be adduced to support it.

DURANT.

Burchell, H. B.: An Evaluation of Esophageal Electrocardiograms in the Diagnosis of Healed Posterior Myocardial Infarction. *Am. J. M. Sc.* 216:492 (Nov.), 1948.

Experience with esophageal electrocardiography in attempting to elucidate the significance of a Q wave in Lead III has been scattered over the past ten years. The use of small but heavy electrodes with thin, flexible lead wires has made the problem easier for the patient, who may either swallow the electrode like a capsule or allow it to pass down the throat when it is introduced through the nose. For comparison of esophageal electrocardiograms made at different levels it has been helpful to use multiple electrodes at fixed distances along the small-caliber flexible plastic tube which carries the insulated lead wires. A group of fifty cases in which esophageal electrocardiograms were made has been chosen for the purpose of determining the probability of obtaining diagnostic tracings in cases in which the history and electrocardiograms at the time of an acute episode indicated previous acute myocardial infarction and in cases in which only angina pectoris or a deep Q₃ was present.

As a result of these studies it has been concluded that electrocardiograms made with the electrode in the lower part of the esophagus and stomach are sometimes of great value in confirming a diagnosis of healed posterior myocardial infarction, but sometimes they are normal or are not definitely diagnostic even when the heart is known to contain a scar in the posterior myocardial wall. Esophageal electrocardiograms which might be regarded as diagnostic of old posterior myocardial infarction, particularly those with QS deflections followed by a deeply inverted T wave, have usually been associated with a suggestive or diagnostic Q_2Q_3 pattern in the standard leads in this study. While the transitional zone through which the types of ventricular complex characteristic of atrial levels and of ventricular levels are obtained is usually narrow, in some instances the former type of complex may tend to persist when the atrial complex contains no intrinsic type of deflection.

When the esophageal leads are used to elucidate the clinical significance of a deep Q_3 in cases in which this is the only finding leading to the suspicion of previous myocardial infarction, the findings are frequently of equivocal nature.

DURANT.

Courter, S. R., Felson, B., and McGuire, J.: Familial Interauricular Septal Defect With Mitral Stenosis (Lutembacher's Syndrome). Am. J. M. Sc. 216:501 (Nov.), 1948.

Familial congenital interauricular septal defect complicated by mitral stenosis is described apparently for the first time by the authors. This disorder was found in two sisters, 21 and 26 years of age, respectively. In a review of the literature the authors were unable to find any mention of familial Lutembacher's syndrome, and also no report of a familial occurrence of uncomplicated interauricular defects.

DURANT.

Porter, W. B.: The Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort. Am. J. M. Sc. 216:509 (Nov.), 1948.

From an extensive experience with the electrocardiogram associated with exercise in cases of angina of effort, an experience which has extended over more than eight years, the author states that the most significant change during induced attacks has been the occurrence of premature ventricular beats in four patients in whom normal rhythm was present before and after the induced episode. Three of these patients had few signs of cardiovascular disease and resting electrocardiograms were equivocal in all four. The premature beats occurred during the period of acceleration of heart rate and at the peak of chest pain, disappearing with rest and cardiac slowing. This is in contrast to the general rule that extrasystoles are increased during the post-acceleration or slowing period following induced tachycardia. It is suggested by the author that the occurrence of premature beats, especially pulsus bigeminus, under these circumstances may have grave prognostic significance. He feels, however, that a larger series of cases must be studied before final conclusions can be drawn. A conservative dose of quinidine sulfate, consisting of 0.2 to 0.4 Gm., given three times daily and equally spaced during the period of physical activity, may be used profitably in these patients since in two of those reported, the exercise tolerance was greatly increased thereby.

DURANT.

D'Alton, C. J., Darling, R. C., and Shea, E.: The Insensible Loss of Water in Congestive Heart Failure. Am. J. M. Sc. 216:516 (Nov.), 1948.

Congestive heart failure is characterized by a marked disturbance in fluid balance. While the failure of the kidneys to excrete water and salt in this condition has been extensively studied, water loss by other routes has been less thoroughly investigated. For this purpose fourteen determinations of the insensible weight loss, partitioned into its several parts, were accomplished. Eight of these were carried out on patients with heart disease, including three comparisons of the same patient before and after recovery from severe decompensation. From these measurements the quantity of insensible perspiration was found not to change significantly when the circulatory status of an individual was altered by cardiac decompensation, although the amount lost by way of the lungs followed the pulmonary ventilation. The absolute quantity of insensible perspiration (skin) in these patients and a few others with various diseases correlated only very roughly with body size, and seemed to be characteristic of the individual. The range of individual measurements was large but well within the reported range in all instances. The palmar sweat secretion and,

by inference, the solar, together contributed little to the total insensible water loss under the conditions of the study, being less than 5 per cent of the total. DURANT.

Schlichter, J. G., Wilburne, M., and Grossman, M.: The Use of Acetylcholine in the Objective Determination of Circulation Time in Man. *Am. J. M. Sc.* 216:523 (Nov.), 1948.

In the course of a study of the effects of acetylcholine, it was noted that an accurate objective determination of the circulation time in unanesthetized normal dogs and anesthetized open-chested animals may be obtained by the use of this substance. The circulation time obtained with this substance is shorter, shows fewer variations, and appears superior to most methods applicable to animals. One distinct advantage is that an unequivocal end point can be determined electrocardiographically.

The results indicated that acetylcholine also offers a clear end point for the objective determination of circulation time in man. The doses used caused varying degrees of sinus slowing or asystole. The minimal dose evoking such response varied in the different patients, but the average was 40 milligrams. Inasmuch as doses of more than 60 mg. were not administered, failure to obtain a circulation time measurement in some patients may have been due to inadequate doses. The action of the drug on the heart, on the basis of animal experiments, appears to be a direct one whereby the acetylcholine passes via the coronary vessels to the sinus node and the A-V junction. A correlation of the circulation time with other clinical and laboratory findings has shown that the normal circulation time varies between 1.2 and 6 seconds. A circulation time over 7 seconds was found to be definitely abnormal. Compared with other methods, acetylcholine yields a distinctly shorter circulation time. The small volume and the short duration of the injection reduces the range of variation seen with the sodium cyanide, thiamine, and Diodrast methods.

The only serious objection to the use of this test for the determination of the circulation time in man is the induction of multiple premature systoles and auricular fibrillation. The latter was observed in two cases. Both of these patients had hypertension and coronary sclerosis and one was also markedly anemic. The margin of safety may be very small. In one case, 20 mg. had no effect whereas 25 mg. produced asystole followed by auricular fibrillation. In both cases in which auricular fibrillation occurred the mechanism was broken and sinus rhythm re-established by the administration of oral quinidine. Atropine injections and oxygen inhalation did not abolish the arrhythmia. It is concluded that while acetylcholine may be used for simple, accurate, and objective measurements of circulation time in man, it cannot be regarded as an innocuous procedure for the patient. DURANT.

Bine, R., Jr., and Friedman, M.: Observations Concerning the Effects of Blood Upon the Action of a Digitalis Glycoside. *Am. J. M. Sc.* 216:534 (Nov.), 1948.

In a previous study, it was found possible, by means of the embryonic duck heart preparation, to detect as little as 0.05 microgram of a digitalis glycoside per cubic centimeter of Tyrode's solution. The extreme sensitivity of this preparation to glycoside in Tyrode's solution suggested the possibility that perhaps minute amounts might be detected in blood also. In order to standardize this type of detection, however, it was thought necessary to determine separately the effects of blood cells and serum of whole blood.

It was found that rat and human blood sera inhibited markedly the effect of the glycoside. This retardation of action, however, was not marked at moderate concentration of the glycoside (1.0 microgram per cubic centimeter), but only at low concentrations (below 1.0 microgram per cubic centimeter). It is suggested that the retardation in serum is not due primarily to the action of the serum on the drug, but rather to the inability of the embryonic heart to respond quickly to a medium low in ionized calcium (about 5.0 mg. per 100 c.c.). It was of particular interest, however, that as little as 0.1 microgram of glycoside in 1.0 c.c. of human serum could be detected by means of the preparation. Perhaps even more important was the finding that the time of occurrence of the "digitalis effect" depended upon the concentration of the glycoside in the serum. This last finding allows the possibility of making quantitative assays of the content in any given serum sample suspected of containing it. DURANT.

Bennett, I. L., Jr., and Hyeman, A.: Paroxysmal Hypertension Associated With Tabes Dorsalis. Report of Three Cases. *Am. J. Med.* 5:729 (Nov.), 1948.

The purpose of this article is to report three additional cases of paroxysmal hypertension associated with tabes dorsalis. In one of the cases presented, the unfamiliarity with this association led to a needless surgical exploration for a pheochromocytoma. The authors point out that gastric crises are not always associated with the bouts of hypertension. Gastric crises were present in only one of their patients and in this instance the attack consisted only of nausea and vomiting unaccompanied by pain. The hypertension was entirely asymptomatic in the second patient and in the third patient the paroxysms of hypertension were not accompanied by symptoms except for occasional associated lightning pains. Penicillin therapy appeared to have a beneficial effect on the hypertensive crises in only one of the patients. They were unable to find any certain means of precipitating hypertension in their patients. The histamine test for pheochromocytoma was uniformly negative. The authors believe that paroxysmal hypertension is simply one of the disturbances of the autonomic nervous system that may occur in tabes dorsalis.

KLINE.

Massey, F. C., and Drake, W. L., Jr.: Spontaneous Rupture of the Heart Due to Myocardial Infarction. *Am. J. Med.* 5:775 (Nov.), 1948.

The authors report the case of a 42-year-old white man who was hospitalized because of a myocardial infarction. Serial electrocardiograms localized the infarction to the anterior surface of the left ventricle. Twelve days after admission the patient was being examined routinely. Suddenly and without warning the patient tensed all his muscles, straightened out rigidly, the neck dropped backward in opisthotonic fashion, and tonic and clonic convulsions shook him for a few seconds. During this time one of the authors was auscultating the heart. No friction rub was heard before this spectacular episode, but immediately after its inception an intense, grating pericardial rub was audible from the third left intercostal space down to the apex. Just prior to the appearance of the pericardial rub auscultation of the heart was interrupted in order that a question might be answered so that if rupture of the ventricle occurred at this instant it was not actually heard. Within three minutes after the onset of the episode the patient was dead. Post-mortem examination of the heart revealed a jagged, vertical tear on the anterior surface of the apex parallel to, and immediately to the left of, the interventricular septum. The defect was 2.5 cm. in length.

KLINE.

House, R. K.: Diffuse Interstitial Myocarditis in Children. *Am. J. Path.* 24:1235 (Nov.), 1948.

The author reviews four cases of diffuse interstitial myocarditis in infants ranging in age from 3 weeks to 13 months. The clinical course was short and was featured by fever, cyanosis, dyspnea, and anorexia. Cardiac enlargement and tachycardia, "low T waves in all leads," pulmonary congestion, and enlargement of the liver suggested some form of myocarditis. These children were well nourished and showed no evidence of congenital defect, nor anything to account for the cardiac hypertrophy found in all cases.

Microscopically there was a diffuse interstitial cellular infiltration, primarily lymphocytic, accompanied by widespread interstitial edema, but little damage to individual myocardial fibers. In two cases there was an additional endocardial fibrosis, but in only one was there any evidence of patchy fibrosis in the myocardium. The lungs in all cases showed a bronchopneumonia which was interpreted as being secondary and terminal.

A review of the history showed that upper respiratory infection had developed in at least three of the four cases. Sulfonamide therapy employed in one case appeared to be a factor too remote for consideration.

All the recorded causes, proved or suspected, in "diffuse interstitial myocarditis" were reviewed and none appeared applicable to these cases. The report is of interest in revealing in infants a type of myocardial disease generally expected in adults. On the other hand, the causative factors remain equally obscure.

GOULEY.

Nahum, L. H., and Hoff, H. E.: Nature of the Precordial Electrocardiogram. *Am. J. Physiol.* 155:215 (Nov.), 1948.

Right and left apical precordial leads were recorded in fifteen dogs at rest, and following warming, cooling, and the application of potassium chloride to various cardiac regions. The authors assume that the precordial electrocardiogram represents a record composed by interference of opposing electrical forces either proximal or distal with respect to the exploring electrode. Their interpretation applies to the QRS deflection as well as to the T wave. The proximal zone represents the area in the immediate vicinity of the precordial electrode (epicardial or endocardial). The distant region usually includes the base of the heart. An intermediate zone is described, which when cooled, warmed, or treated with potassium chloride, influences the precordial electrocardiogram but little. As the electrodes were placed at the apical area, precordial electrocardiograms of the kind obtained are interpreted as base-apex interference records.

HECHT.

Parson, Wm., Mayerson, H. S., Lyons, C., Porter, B., and Trautman, W. V., Jr.: Effect of the Administration of Adrenalin on the Circulating Red Cell Volume. *Am. J. Physiol.* 155:239 (Nov.), 1948.

Simultaneous plasma and red cell volume determinations, using T-1824 and radiolabelled red cells, were performed on five subjects following the subcutaneous injection of 1.0 mg. of adrenalin. A good clinical epinephrine response was noted in all, but no changes in plasma volume, red cell volume, total blood volume, hematocrit readings, hemoglobin, and plasma protein concentration could be demonstrated. It is assumed that in man no appreciable blood cell reserves are available for emergency mobilization.

HECHT.

Mayerson, H. S., Lyons, C., Parson, Wm., Nieset, R. T., and Trautman, W. V., Jr.: Comparison of Results of Measurements of Red Blood Cell Volume by Direct and Indirect Technics. *Am. J. Physiol.* 155:252 (Nov.), 1948.

Determining the volume of packed red cells, the use of radioactive red cell measurements with P_{22} and the determination of plasma volume with T-1824 yielded concomitant measurements of red cell mass, plasma volume, and total blood volume in ten normal subjects and in thirty-five patients suffering from a variety of diseases not directly related to the cardiovascular system. If the hematocrit values were corrected for plasma trapped between the cells by a factor 0.915, good agreement was obtained between the "true" blood volume obtained from determinations by red cell- P_{22} and dye-plasma methods and blood volumes obtained from corrected hematocrit readings and either red cell or plasma volume determination. It is assumed that the amount of blood present in the small vessels (with generally lower hematocrit values) is not large enough to affect greatly the estimation of blood volume calculated from the dye and the corrected hematocrit reading under relatively normal conditions.

HECHT.

Berenson, G.: Value of Routine Fluorograms as a Measure for Detecting Cardiac Abnormalities. *Am. J. Pub. Health* 38:1564 (Nov.), 1948.

This is the report of 14,235 miniature films (35 mm.) taken as routine fluorograms of marine and naval personnel at a military camp in North Carolina in 1947. Although the ages varied from 17 to 60 years, the majority were young marines just entering military life. In thirty-one subjects cardiovascular abnormalities were noted. In eighteen of these, including three civilians, cardiac enlargement on a hypertensive basis was present. Three instances of dextrocardia without situs inversus were noted. Two patients had a funnel chest causing enlargement. Dextro-position of the aorta and coarctation were present in one patient each. Various aortic and mitral configurations were seen. Twenty-two patients had noncardiovascular diseases of the chest, including pulmonary tuberculosis in ten patients.

The author concludes that it is possible to detect cardiac abnormalities on routine fluorograms, accurate diagnosis requiring confirmation by further clinical investigation. It is suggested by this series that the number of patients with demonstrable cardiac abnormalities in routine fluorograms is greater than the number of persons with tuberculosis in a given population. The author, therefore, emphasizes the importances of discovery of heart disease by mass fluorography.

WAIFE.

Moyer, J. H., and Ackerman, A. J.: Hereditary Hemorrhagic Telangiectases Associated With Pulmonary Arteriovenous Fistula in Two Members of a Family. *Ann. Int. Med.* 29:775 (Nov.), 1948.

The authors describe the physical, radiologic, and laboratory findings in two brothers 29 and 26 years of age, respectively, in whom a clinical diagnosis of pulmonary arteriovenous fistula complicating hereditary hemorrhagic telangiectases was made. In each instance, the diagnosis of the pulmonary lesion was confirmed by angiographic studies. In the older of the two brothers, cyanosis, clubbing of the fingers, hyposaturation of the blood with oxygen, compensatory polycythemia, increased blood volume, and extracardiac murmurs were lacking. By contrast, in the younger brother, all these findings were present. This difference was attributed to the larger communications which were demonstrable between the pulmonary arteries and veins in the latter instance, which resulted in an increased amount of unaerated blood being shunted back to the left heart. In the cyanotic patient, all the primary and secondary manifestations of the venous-arterial shunt were completely eliminated following a successful unilateral pneumonectomy.

The authors emphasize the association of these pulmonary vascular lesions with hereditary hemorrhagic telangiectases of the skin and relate them both to a common congenital fault which results in the formation of new vascular buds with consequent direct communications between arterioles and veins which circumvent the normal capillary bed.

WENDKOS.

Levine, H. D.: Abnormal Rapid Rhythms Associated With Digitoxin Therapy. *Ann. Int. Med.* 29:822 (Nov.), 1948.

By means of serial electrocardiographic records in seven patients who had received varying amounts of digitoxin for the treatment of heart failure, it was possible to demonstrate that serious rhythms, such as ventricular tachycardia and A-V dissociation, can result from the toxic action of this drug. In most instances, excessive amounts of the drug could be held responsible, but in a few of the cases, the patients were receiving doses which are ordinarily considered to be therapeutic. As with crude digitalis preparations, the toxic rhythms produced by digitoxin developed at times without any of the usual premonitory gastrointestinal or visual disturbances indicative of digitalis intoxication. Their occurrence should, therefore, be suspected when, in the presence of auricular fibrillation, a previously irregular ventricular rhythm suddenly becomes regular or when, in the presence of normal sinus rhythm, the rate should suddenly accelerate.

WENDKOS.

Massie, E., Huguley, C. H., and Stillerman, H. S.: The Heart in the Terminal State: Effect of Intracardiac Epinephrine. *Ann. Int. Med.* 29:838 (Nov.), 1948.

Electrocardiograms were taken on thirty-four patients before, at the time of, and after clinical death. Slowing of the cardiac rate was almost a constant finding with subsequent sino-auricular node depression and resultant auriculoventricular nodal rhythm appearing in over one-third of the cases. Auriculoventricular and intraventricular block in various degrees was extremely common. Evidences of ventricular irritability were manifested by the frequent occurrences of ventricular fibrillation, tachycardia, and flutter along with ventricular extrasystoles from single and multiple foci. Auricular fibrillation did not appear terminally except in those instances where it had been present previously. The terminal complex in the electrocardiogram represented ventricular activity in twenty-seven patients and auricular activity in seven. The terminal ventricular complexes often assumed bizarre shapes with marked variation in form, amplitude, and duration.

Attempts at cardiac resuscitation with intracardiac epinephrine following cessation of heart activity were made in eighteen patients, including eleven attempts in which the drug was injected into the cardiac chambers and nine in which it was infiltrated into the ventricular myocardium. The latter method was more successful, producing an effect in five patients (56 per cent), whereas the former accounted for only two responses (18 per cent). In only two patients was there restoration of regular ventricular beats; in one of these the cardiac activity continued for thirty-six minutes after respiration had ceased. The authors suggest that if intracardiac epinephrine is to be life-saving, it should be given, if possible, before complete cardiac cessation occurs and before the heart muscle and vital cerebral centers have been deprived of oxygen for too long a period.

WENDKOS.

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NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES TO BE HELD IN WASHINGTON IN JANUARY

A National Conference on Cardiovascular Diseases will take place in Washington, D. C., January 18-20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute. Dr. H. M. Marvin, President of the Association, and Dr. C. J. Van Slyke, Director of the National Heart Institute, will be the Co-Chairmen.

The purpose of the Conference is "to investigate, define and develop immediate and long-range programs designed to meet the problems of research, education, and community service posed by diseases of the heart and circulation, and to coordinate the efforts of all groups concerned with these problems, with a view to gaining the most effective use of their resources for all the members of the community."

Dr. Paul D. White, Executive Director of the National Heart Institute, was elected Chairman of a steering committee to plan the Conference. Dr. White is a former President of the American Heart Association.

The Conference is to be comprised of members representing the various medical disciplines and the ancillary professional fields concerned with a cardiovascular program. It will have three main sections: Technical Knowledge and Research, Community Service, and Education. Described as a "working," not a "talking" Conference, the three-day meeting is expected to develop a concrete program of action to correlate an all-out national attack on the heart disease problem embracing the resources of all voluntary and official agencies in the field.

EXECUTIVE COMMITTEE MEETING

A new set of recommended standards and minimum requirements for cardiovascular clinics has been prepared by the Cardiovascular Clinic Committee and will be presented to the Board for approval at its December meeting.

Dr. Paul D. White was appointed the Association's official delegate, and Dr. H. M. Marvin, deputy, to the First International Congress on Cardiology to be held in Paris in September, 1950.

Dr. Frederick Lewy has been employed to carry out a two-year study of community rheumatic fever programs for the American Council on Rheumatic Fever.

New affiliated heart associations approved, in addition to those listed in the October issue, include the Massachusetts Heart Association and the Middle Tennessee Heart Association.

A. W. ROBERTSON CHAIRMAN OF 1950 HEART CAMPAIGN

Mr. A. W. Robertson, of Pittsburgh, serving his second term as Chairman of the Board of the Association, has consented to be General Campaign Chairman of the 1950 Heart Campaign. Mr. Robertson is Chairman of the Board of Westinghouse Electric Corporation and has long been active in civic and welfare activities.

Mr. Winthrop W. Aldrich will again serve as Campaign Treasurer, and Secretary of Labor Maurice Tobin, as Chairman of the Labor Committee.

GRANTS-IN-AID FOR RESEARCH

Applications for grants-in-aid for cardiovascular research in 1950-1951 must be filed by December 15, 1949. A total of forty-nine applications for Research Fellowships and Established Investigators had been received by the September 15 deadline.

American Heart Journal

VOL. 38

DECEMBER, 1949

No. 6

Original Communications

ATRIAL SEPTAL DEFECT. A STUDY OF INTRACARDIAC SHUNTS, VENTRICULAR OUTPUTS, AND PULMONARY PRESSURE GRADIENT

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DURHAM, N. C.

PATIENTS with atrial septal defect provide an unusual opportunity for the study of certain problems connected with the regulation of cardiac output and the hemodynamics of the pulmonary circulation. It is frequently possible to pass a catheter through the septal defect into the venous side of the pulmonary circulation. Blood samples and pressure determinations from this site extend the significance of the usual observations which can be made in the course of an intracardiac catheterization. It is possible to determine the pressure gradient through the pulmonary vascular tree, to estimate the right and left ventricular outputs, to estimate the magnitude and direction of intracardiac shunts, and to observe changes in some of these quantities as a result of exercise or other stimuli. This paper reports observations on four patients with atrial septal defect in whom it was possible to catheterize pulmonary veins.

METHODS

Intracardiac catheterization was performed by a method previously described.¹ Oxygen consumption was measured by timed collection of expired air in Douglas bags, volume measurements in a Tissot spirometer, and analysis in the Haldane apparatus. Blood samples for oxygen analysis were collected under oil with oxalate as an anticoagulant or were drawn into oiled, heparinized syringes and stored in ice. Oxygen analyses were carried out by the method of Van Slyke. Duplicate analyses were required to check within 0.1 volume per cent. In Case 2, blood oxygen contents were determined by a spectrophotometric method.² Pressure measurements in the heart were made through the catheter by Hamilton manometer, the point of zero reference being taken as 5.0 cm.

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This work was supported by grants from the Life Insurance Medical Research Fund and the Anna H. Hanes Fund of Duke University.

below the fourth costochondral junction. Mean pressures were determined by planimetry. Arterial blood was obtained from the brachial artery through an inlying needle. All determinations were made while the patient was in a supine position. Exercise was carried out by alternately flexing and extending both legs together at a constant rate. No determinations were made until exercise had been continued for at least three minutes. Exercise studies were preceded by observations made at rest during the same catheterization. In the case of J. C. (Case 3) the pulmonary venous pressure and oxygen content of pulmonary venous blood reported during exercise were determined at the same study in a separate exercise period, which resembled as closely as possible the exercise period during which the remaining determinations were made.

CASE HISTORIES

CASE 1.—A. L., a white man, 37 years old, had noticed as a child that he was unusually short of breath on exertion. In the last ten years exertional dyspnea had gradually become worse and for two years there had been frequent episodes of lower respiratory tract infection and a chronic cough. He had not had ankle edema. Examination showed moderate cyanosis. The fingers were clubbed. The heart was moderately enlarged. The rhythm was regular. Along the left sternal border in the third to fifth intercostal spaces there was a low-pitched, long diastolic murmur of moderate intensity. Roentgenograms showed an enlargement of the pulmonary conus and a dilatation of the pulmonary arteries, that on the left being of aneurysmal proportions. The diagnosis of atrial septal defect was made by intracardiac catheterization (see Table 1).^{*} Two months later the left pulmonary aneurysm was wrapped with Cellophane. At the time of the second catheterization, one year later, the patient's symptoms and physical findings were substantially unchanged, except that there had been a decrease in the frequency and severity of respiratory infections.

CASE 2.—N. Q., a white girl, 12 years of age, had been entirely asymptomatic. She was referred for study after discovery of a heart murmur in a routine examination. There was a precordial systolic murmur maximal in the second and third intercostal spaces at the left sternal border. The pulmonary conus was enlarged, and the vascular markings at the lung roots were accentuated. There was right axis deviation. The fingers were not clubbed.

CASE 3.—J. C., a white diabetic man, 31 years old, had had moderate nonprogressive exertional dyspnea for many years. Seven years before the present study, examination disclosed a harsh systolic murmur maximal in the pulmonic area and transmitted down the left sternal border. The pulmonic second sound was louder than the aortic. Roentgenograms showed prominence of the pulmonary conus and the pulmonary vascular markings. There was right axis deviation. The fingers were not clubbed, and there was no cyanosis. At the time of the present study there had been no significant change in these findings. The diagnosis of atrial septal defect was made by intracardiac catheterization.

CASE 4.—C. D., a Negro man, 24 years old, had been well until three years before the present study. At that time he developed pain in both knees, lasting two to three weeks. Shortly thereafter he began to have brief spells of unconsciousness, unrelated to posture. For a time these were frequent, but there had been none for six months before study. For six to eight months there had been slowly progressive exertional dyspnea. There was a transient episode of ankle edema. Examination showed moderate clubbing of the fingers. There was a prominent pulsation of the neck veins with cardiac systole. Fluoroscopy showed generalized cardiac enlargement, including both atria, and increased pulmonary vascular markings. There was complete heart block with a ventricular rate of 32 to 36 per minute and right axis deviation. The pulmonary

^{*}The first study was conducted by Dr. James V. Warren of Emory University, who has kindly made the data available.

second sound was accentuated. Over the precordium there was a harsh, blowing systolic murmur. At the apex a low-pitched diastolic murmur was inconstantly heard. On the basis of these findings and observations made during intracardiac catheterization, the diagnoses of atrial septal defect and possible mitral disease were made.

OBSERVATIONS

The data obtained by intracardiac catheterization of these patients are presented in Table I. Calculations made from the data appear in Table II.

Calculations.—In determining percentage saturation no correction is made for dissolved oxygen. The accuracy of the measurement in this study is not sufficient to warrant such a correction. For reasons of economy, blood for oxygen capacity was not drawn with each appropriate sample. The values for percentage saturation are therefore to be regarded as approximate. For example, the figure of 100 per cent for percentage saturation of pulmonary venous blood in A. L. (Case 1) is clearly incorrect. Here, the result has been taken to indicate normal oxygenation of the blood, and a pulmonary venous saturation of 97 per cent³ has accordingly been used for calculating results in the preceding study on this patient. This approximation involves little error in subjects with a large arteriovenous difference across the lungs, but would not be admissible in the ordinary case, where the A-V difference is quite small (see the following).

The right ventricular output in cases of atrial septal defect is obtained by dividing the oxygen consumption by the arteriovenous difference across the lungs:

$$RVO \text{ (Liters per minute)} = \frac{O_2 \text{ consumed (cubic centimeters per minute)}}{\text{Pulmonary venous oxygen content} - \text{pulmonary arterial oxygen content (cubic centimeters per liter)}}$$

This calculation assumes that pulmonary collateral circulation is insignificant.

The left ventricular output can be approximated by dividing the oxygen consumption by the arteriovenous difference across the heart:

$$LVO \text{ (Liters per minute)} = \frac{O_2 \text{ consumed (cubic centimeters per minute)}}{\text{Arterial oxygen content} - \text{mixed caval oxygen content (cubic centimeters per liter)}}$$

This equation neglects the contribution from the coronary sinus. The exact mixed caval content is, of course, not available. However, data of Brannon and co-workers⁴ indicate that the oxygen contents of superior and inferior caval blood in cases of atrial septal defect at rest do not usually vary by more than 1.0 vol. per cent. Accordingly, the superior caval oxygen content was used in estimating the resting left ventricular output, except in Case 2, in which values for superior and inferior caval blood are averaged. Such an approximation would not be valid for subjects carrying out leg exercise. No estimate of left ventricular output during exercise is possible from the data presented in Table I.

Because of the probability of a small right-to-left shunt and the possibility of coexistent pulmonary vascular disease, calculation of the right ventricular

TABLE I

CASE	STATE	SUR- FACE AREA (SQ. M.)	O ₂ CON- SUMP- TION (C.C. PER MIN.)	PRESSURE (MM. Hg)						BLOOD OXYGEN CONTENT (VOL. PER CENT)											
				RIGHT ATRIUM	LEFT ATRIUM	PUL- MON- ARY VEIN	PULMONARY ARTERY			SYSTEMIC ARTERY			SU- PERIOR VENA CAVA	RIGHT ATRIUM	LEFT ATRIUM	PUL- MON- ARY VEIN	PUL- MON- ARY ARTERY	SYS- TEMIC ARTERY	SATUR- ATION	SATURA- TION ARTERIAL BLOOD	PER CENT SATURATI- ON PULMONA- RY VENOUS BLOOD
							SYS- TOLIC	DIAS- TOLIC	MEAN	SYS- TOLIC	DIAS- TOLIC	MEAN									
L.	Rest	1.59	215	0.5*	1.0*		113†			116	68	79	14.3	14.4	21.9		17.5†	22.0	25.4	87	
	Rest ¹	1.60	183	4	6	6	93	50	65	96	63	78	14.2	14.2	20.3	22.8	15.8	18.2	22.8	80	"100"
Q.	Rest	1.16	188	3		4	22	9	16				11.5 ²	15.0		15.8	14.9	15.6	16.2	96	98
	Rest	1.60	269	6		7	30	9	20	132	81	101	11.4	13.0		16.7	14.9	15.7	18.0	87	93
C.	Exercise		457	2		5	36	12	23	151	84	113	14.5			16.9	14.2	16.6		92	94
	Rest ³		306	18			52	14	25	145	95	115	12.5	17.0			18.2	19.8	21.8	91	
D.	Rest	1.73	239	16		19	58	8	23	158	93	120	11.1	16.7		20.1	18.5	19.6	22.6	87	89
	Exercise		536	30			95	23	45	184	92	125					15.2	19.3		85	

*Saline manometer.

†Right ventricle.

¹One year after first study.²Inferior vena caval blood: 11.8 vol. per cent.³Separate study.

TABLE II

CASE	STATE	LEFT VENTRICULAR OUTPUT (L. PER MIN.)	RIGHT VENTRICULAR OUTPUT (L. PER MIN.)	PULMONARY PRESSURE GRADIENT (MM. HG)	PULMONARY RESISTANCE (PULMONARY GRADIENT PER RIGHT VENTRICULAR OUTPUT) (MM. HG PER L. PER MIN.)	RIGHT-TO- LEFT SHUNT (L. PER MIN.)	LEFT-TO- RIGHT SHUNT (L. PER MIN.)	$\frac{1-X^*}{Y^\dagger}$	EFFECTIVE PULMONARY FLOW (L. PER MIN.)
A. L.	Rest	2.8	3.2 ¹			0.7	1.0	.34	2.2
	Rest ²	4.6	2.6	59	22.7	2.4	0.5	.65	2.1
N. Q.	Rest	4.7	19.8	12	0.61	0.2	15.3	.23	4.5
J. C.	Rest	6.3	14.9	13	0.87	1.2	9.8	.56	5.1
	Exercise		16.9	18	1.06			.11	
C. D.	Rest ³	4.2							
	Rest	2.8	14.9	4	0.27	0.2	12.2	.33	2.7
	Exercise ⁴		10.9	12	1.10			.16	

*1-X = Fraction of aortic blood which is caval in origin.

†Y = Fraction of pulmonary arterial blood which is caval in origin.

¹Assuming pulmonary venous blood to be 97% saturated (see text).²One year later.³Separate study.⁴Calculations utilize resting pulmonary venous oxygen.

The effective pulmonary flow, as defined by Bing,⁶ is estimated from the expression $\frac{O_2 \text{ consumption}}{PV-VC}$. This represents the flow rate of caval blood which passes through the pulmonary bed, and is therefore equal to $Y(RVO)$. It is also that portion of the left ventricular output which is contributed from the pulmonary veins and is therefore equal to $X(LVO)$.

The data are inadequate for calculation of shunts during exercise because there is no information as to the oxygen content of the mixed caval blood. However, an index of change in the proportional values of the shunts is provided by

the expression $\frac{1-X}{Y} = \frac{PV-A}{PV-PA}$, that is, the ratio of the caval fraction of the

aortic blood to the caval fraction of the pulmonary arterial blood. A decrease in this ratio indicates a decrease in the proportional size of the shunts, that is, a decrease in right-to-left shunt, a left-to-right shunt, both shunts together, or a proportional fall in one shunt large enough to mask a rise in the other. The interpretive value of this ratio is quite limited, but a change in the ratio does indicate a change in the proportional value of the shunts.

Interatrial Shunts and Ventricular Outputs.—The existence of a large left-to-right shunt in patients with atrial septal defect has long been regarded as reasonably certain,^{7,8} but direct evidence for the shunt was first provided by Brannon and associates,⁴ who found large quantities of oxygenated blood entering the right atrium. This observation has been amply confirmed. The existence of a small right-to-left shunt is indicated by the present data. This has been suspected clinically and was anticipated by Cournand from an analysis of pressure curves in the two atria during the cardiac cycle.⁹

There is almost no information on changes in ventricular outputs and shunts in response to various stimuli. The occurrence of cyanosis in congestive failure and on exercise in some patients has been taken to indicate an increased right-to-left shunt.⁶ However, Burchell and Wood¹⁰ suggest that this may result, in cyanotic forms of congenital heart disease, from a fall in oxygen content of the shunted venous blood rather than an increase in the shunt itself. They have found that venous shunts in a variety of anatomic conditions have remained remarkably constant for each patient under varying environmental conditions of stress and over a period of time. This is apparently not always the case in atrial septal defect. The shunts of A. L. (Case 1) changed significantly between the two studies. The data on J. C. (Case 3) and C. D. (Case 4) indicate a change in absolute as well as proportional values of the shunts from rest to exercise.

Proportional change in shunts is indicated by the changes in the ratio $\frac{1-X}{Y}$,

which fell during exercise in each case. Other considerations indicate that the absolute values must have changed, as well. In J. C. (Case 3) exercise produced no significant change in pulmonary venous oxygen or right ventricular output, but a rise in systemic arterial oxygen almost to the pulmonary venous level.

output should employ data from pulmonary venous blood rather than arterial blood or an assumed value for normal saturation. With a large right ventricular output the arteriovenous difference across the lungs may be quite small, and an error in its determination will produce a relatively large error in the output estimation. Since the left ventricular output is usually much smaller than the right, a similar error in estimating oxygen content of mixed caval blood will produce a much smaller absolute error in estimation of the left ventricular output. For example, C. D. (Case 4) at rest had a right ventricular output of 14.9 liters per minute and a left ventricular output of 2.8 liters per minute. An error of 1.0 vol. per cent in estimation of pulmonary venous oxygen content would yield a right ventricular output of 9.2 or 39.8 liters per minute, while a similar error in estimating mixed caval oxygen content would yield a left ventricular output of 2.5 or 3.2 liters per minute, depending upon the direction of error.

Calculation of the shunts may be made from the general formulas presented by Dexter and associates.⁵ For the present specific problem a simpler treatment appears adequate. Each side of the heart may be considered separately. The aortic blood is a mixture of pulmonary venous blood and of caval blood, from the right-to-left shunt. If the oxygen content of blood from these two regions be known, as well as the oxygen content of the mixture in the aorta, one can determine what fraction of the aortic mixture is caval in origin. Let $I-X$ be the caval fraction; the remainder, X , will then be the pulmonary fraction. Let the oxygen content of aortic blood be A , caval blood VC , and pulmonary venous blood PV . The composition of A as a mixture can then be described as

$$A = (I-X)VC + X PV.$$

Solving for X ,

$$X = \frac{A-VC}{PV-VC},$$

and for $I-X$,

$$I-X = \frac{PV-A}{PV-VC}.$$

The minute volume of the right-to-left shunt is the product of the caval fraction and the left ventricular output, $(I-X) (LVO)$.

In a similar way, the oxygen content of pulmonary arterial blood, PA , results from a mixture of pulmonary venous blood and caval blood. If $(I-Y)$ be the fraction of the pulmonary arterial blood contributed by the pulmonary veins, then the remainder, Y , will be the fraction which is caval in origin. Again,

$$PA = (I-Y)PV + YVC.$$

Solving for Y ,

$$Y = \frac{PV-PA}{PV-VC},$$

and for $I-Y$,

$$I-Y = \frac{PA-VC}{PV-VC}.$$

The minute volume of the left-to-right shunt is the product of the pulmonary fraction and the right ventricular output, $(I-Y) (RVO)$.

The effective pulmonary flow, as defined by Bing,⁶ is estimated from the expression $\frac{O_2 \text{ consumption}}{PV - VC}$. This represents the flow rate of caval blood which passes through the pulmonary bed, and is therefore equal to $Y(RVO)$. It is also that portion of the left ventricular output which is contributed from the pulmonary veins and is therefore equal to $X(LVO)$.

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Proportional change in shunts is indicated by the changes in the ratio $\frac{1-X}{Y}$, which fell during exercise in each case. Other considerations indicate that the absolute values must have changed, as well. In J. C. (Case 3) exercise produced no significant change in pulmonary venous oxygen or right ventricular output, but a rise in systemic arterial oxygen almost to the pulmonary venous level.

This combination of events can result only from a change in the absolute quantity of shunted blood. In the case of C. D. (Case 4) the total right ventricular output during exercise falls below the resting left-to-right shunt, clearly indicating a considerable decrease in the latter during exercise.

The right ventricular outputs of J. C. and C. D. are quite large at rest. During exercise there is little change in the right ventricular output of J. C., while there is a definite fall in that of C. D. In J. C. there was a definite fall in right atrial pressure during exercise, and in C. D. a very large rise, indicating that changes in right ventricular output were not primarily dependent on changes in atrial pressure. Atrial pressures could not be controlled by determination of the intrathoracic pressure, but it seems doubtful that atrial pressure changes of these magnitudes could result from intrathoracic pressure changes alone, with only a moderate increase in pulmonary ventilation. In normal man, exercise and pulmonary ventilation of this extent produce no significant change in atrial pressure.¹¹ The left ventricular outputs during exercise are not yielded by the data. Clinical evidence would suggest that they increased. In general, patients who have not been in frank failure and are able to walk at a moderate rate without discomfort will show an increase in cardiac output on mild exercise.¹¹ In the case of C. D. a separate study indicated that the left ventricular output could be increased, at least moderately (Table II).

In summary, there is evidence that proportional and absolute values of the shunts can change spontaneously and in response to exercise; that the change during exercise in two cases was in the direction of an over-all decrease in the proportional magnitude of the shunts; that the right ventricular output may fall or remain substantially unchanged during exercise in the face of a probable rise in the left ventricular output; and that changes in right ventricular output can be independent of changes in right atrial pressure. These findings suggest that the dynamics of atrial septal defect are not determined simply by atrial pressure levels.

Dexter¹² and Cournand⁹ have found that left atrial and pulmonary venous pressures in hearts with atrial septal defect are slightly higher than right atrial pressures, and this is confirmed by the present results. It has been suggested that this pressure differential is the cause of the shunt.^{7,8} It would appear, however, that if the shunt exists, the pressure differential must exist and that more information is needed before positions of cause and effect are assigned. It is possible (1) that the normal filling pressures of the two ventricles are different; (2) that atrial pressure is an important factor in setting the level of the cardiac output; (3) that other factors affect output of the two ventricles to a roughly comparable degree, and, therefore; (4) when the two atria communicate, that ventricle which normally operates under the lower pressure more readily accepts the available blood and has the larger output. Information is still inadequate on the first and third of these propositions. On the other side, there is adequate evidence that the cardiac output in man may vary widely without apparent relation to the atrial pressure, and that, in fact, the atrial pressure level in many situations is not the dominant factor in determining the cardiac output.¹³ The unequal ventricular outputs in atrial septal defect could well depend upon some factor other than atrial pressure. In this case the predominant shunt and the atrial pressure gradient would be secondary to the difference in ventricular outputs. No conclusive evidence supports either view. The present study of

changes in ventricular outputs and shunts indicates that the dynamics of hearts with atrial septal defects are not determined simply by atrial pressure levels.

The Pulmonary Pressure Gradient.—Although the pulmonary arterial pressure can be determined easily in man by intracardiac catheterization, direct determinations of pulmonary venous pressure are ordinarily not possible. For this reason, interpretation of pulmonary vascular changes by means of changes in pulmonary arterial pressure is uncertain. In congestive heart failure the problem arises as to whether high pulmonary arterial pressures, increasing on exercise, are to be ascribed to a rise in pulmonary vascular resistance, to elevation of left atrial pressure, or to both. The same problem exists with the slight changes in pulmonary pressure sometimes seen in normal individuals during exercise. In the more marked changes described by Motley and co-workers¹⁴ for normal subjects during anoxia, the magnitude of the pressure rise and parallel studies in animals¹⁵ suggest that an increase in pulmonary vascular resistance does occur.

In the present study the opportunity arose to make observations on the pulmonary pressure gradient (that is, the difference in pressure between pulmonary artery and vein) in four subjects, with a comparison of the gradient at rest and exercise in two subjects. The determination of the gradient should be unaffected by the intrapleural pressure, since this presumably has an equal influence on the measurement of atrial and pulmonary arterial pressures. The data obtained are presented in Table I, and the pressure gradient and "pulmonary resistance," in Table II. The calculation of pulmonary resistance is made, according to Aperia,¹⁶ in terms of the ratio of mean pressure to flow, but the resistance is expressed in millimeters of mercury per liter per minute, rather than in absolute units. Pulmonary resistance is used in an attempt to compensate for pressure changes which result from changes in volume flow. A rise in this figure is taken to indicate pulmonary vascular constriction, while a fall indicates dilatation or opening of new channels. The ability of normal man to increase greatly the pulmonary blood flow during exercise with minimal increase in pulmonary arterial pressure¹³ suggests that pulmonary resistance normally falls during exercise.

Three of the subjects show some degree of pulmonary hypertension at rest, while one (N. Q.) does not. N. Q. was able to pass approximately 20 liters per minute through the pulmonary bed under a pressure gradient of 12 mm. of mercury.

In J. C. one-third of the pulmonary arterial pressure (7.0 mm.) and in C. D. 5.6 of the pressure (19 mm.) was contributed by the pulmonary venous pressure. In both cases the pulmonary blood flow was large. The resistance of J. C. (0.87 mm. Hg per liter per minute) is probably near normal; that of C. D. (0.27 mm. Hg per liter per minute) is extremely low. This patient, with an atrial septal defect and possible mitral disease, was able to pass 15 liters of blood per minute through the pulmonary circulation under a pressure gradient of only 4.0 mm. of mercury. Pressure tracings from C. D. are shown in Fig. 1. In A. L., by contrast, there is considerable pulmonary hypertension (mean pressure 65 mm. Hg), to which the pulmonary venous pressure makes a relatively insignificant contribution. The pulmonary flow is quite low with a resultant high resistance (22.7 mm. Hg per liter per minute), about eighty times that of C. D. Pressure tracings from this patient appear in Fig. 2. Obliterative pulmonary arterial disease has been described in patients with atrial septal defect.^{7,8,17}

Pulmonary hypertension in A. L. appears to be on the basis of arterial disease; in C. D. it results entirely from transmitted left atrial pressure. In the three patients without evident pulmonary vascular disease very large flow rates can be maintained through the pulmonary bed under an extremely low pressure gradient. This great distensibility emphasizes the degree to which pulmonary vascular disease must progress before pulmonary hypertension appears at rest in subjects with a normal pulmonary flow.

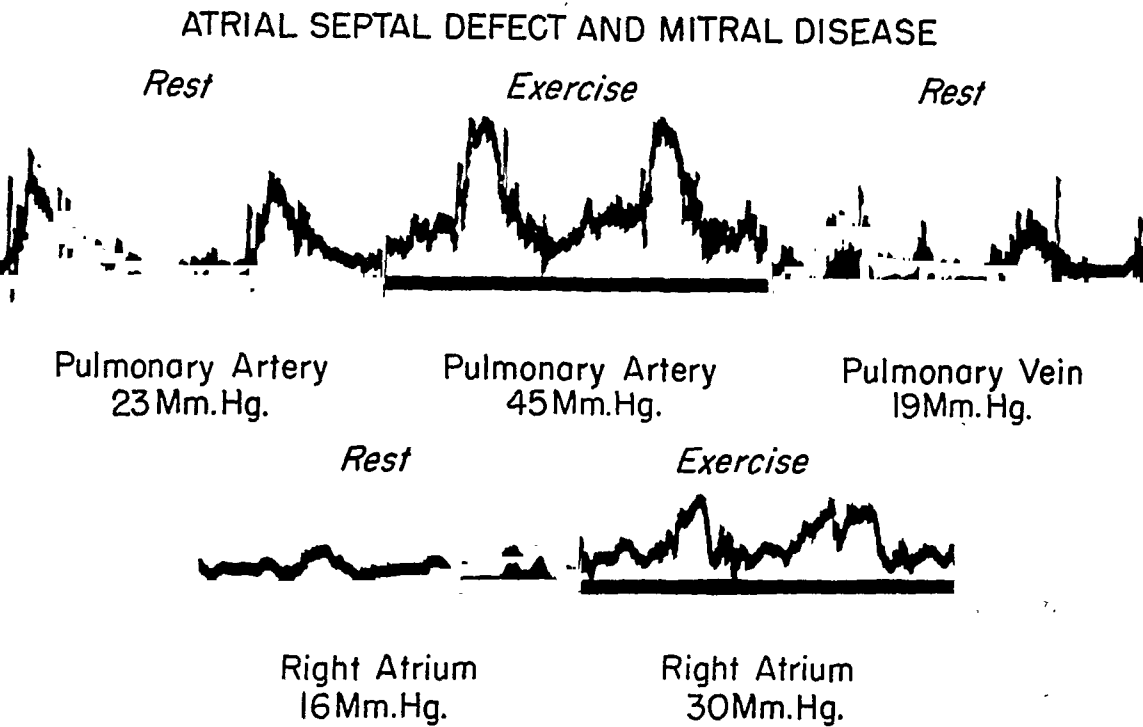


Fig. 1.—Intracardiac pressure tracings from C. D., with atrial septal defect and possible mitral disease. Indicated pressures are mean values. Tracings illustrate the large contribution to pulmonary arterial pressure made by the atrial pressure at rest and during exercise in a subject with pulmonary vascular engorgement.

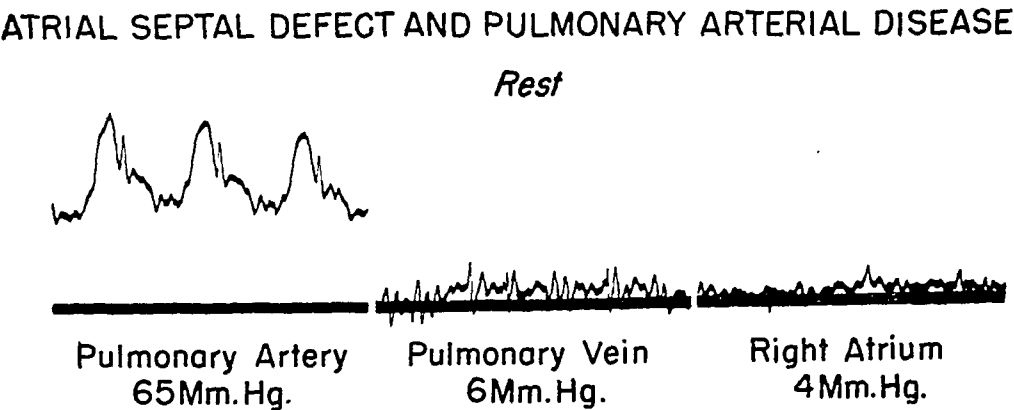


Fig. 2.—Intracardiac pressure tracings from A. L., with atrial septal defect and pulmonary vascular disease. Indicated pressures are mean values. Tracings illustrate pulmonary hypertension based on a high pulmonary vascular resistance.

During exercise, the resistance rose in both J. C. and C. D. In the former, the rise was only 20 per cent; in the latter, 300 per cent. In C. D. the pulmonary venous pressure was not measured during exercise but was estimated to be 3.0 mm. Hg higher than the right atrial pressure, as at rest. It was probably no higher because the left-to-right shunt decreased during exercise. A lower figure would give even a greater increase in gradient and a greater resistance during exercise.

The effect of exercise on the pulmonary circulation of C. D. is of particular interest. In certain respects the findings are similar to those of a subject with left ventricular failure; the pulmonary arterial pressure is elevated at rest and becomes still more elevated during exercise in spite of a decreased pulmonary blood flow.¹³ In this case the abnormal elevation of pulmonary arterial pressure at rest proves to be based on a high pulmonary venous pressure. The small pressure difference between artery and vein suggests a widely dilated pulmonary vascular tree. On exercise, the pulmonary arterial pressure is doubled. The major part of the rise in arterial pressure results from a rise in pulmonary venous pressure. However, the gradient is tripled, and there is a fourfold increase in pulmonary resistance. An opposite result might have been expected from passive dilatation of the vascular tree by increased pressure through its whole course. It is not clear whether the increase in pulmonary vascular resistance results from arteriolar constriction, narrowing of the capillary lumen by edema of the vessel wall, or some other mechanism. The result does suggest that the pulmonary hypertension of exercise in subjects with pulmonary vascular engorgement may result largely from an increased pulmonary venous pressure, but also may be caused in some part by an increased pulmonary vascular resistance.

SUMMARY AND CONCLUSIONS

1. Data are presented on four patients with atrial septal defect in whom it was possible to extend the usual intracardiac catheterization studies by entering the pulmonary veins and, as a result, to estimate the separate ventricular outputs and intracardiac shunts and to determine the pulmonary pressure gradient and pulmonary vascular resistance.

2. The proportional and absolute values of the intracardiac shunts can change spontaneously and in response to exercise. During exercise, changes in right and left ventricular outputs may not parallel each other and may even be opposite in direction. Changes in right ventricular output may be opposite in direction to changes in right atrial pressure.

3. The pulmonary pressure gradient and right ventricular output were measured in four subjects at rest, and in two during exercise. In two subjects with apparently normal pulmonary vessels the pulmonary vascular resistance was extremely low (0.6 to 0.9 mm. Hg per liter per minute). These subjects maintained pulmonary blood flows of 15 to 20 liters per minute under pressure gradients of 12 to 13 mm. of mercury. One subject with pulmonary vascular engorgement had a pulmonary flow of 15 liters per minute with a pressure gradient of only 4.0 mm. of mercury.

4. During exercise the subject with pulmonary vascular engorgement developed pulmonary hypertension. This was primarily due to an increase in left atrial pressure, but there was also a significant rise in the pressure gradient and in the pulmonary vascular resistance.

REFERENCES

1. Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization. Normal Values With Observations on the Effect of Anxiety and Tilting, *J. Clin. Investigation* **24**:326, 1945.
2. Hickam, J. B., and Frayser, R.: Spectrophotometric Determination of Blood Oxygen Content, *J. Biol. Chem.* **180**:457, 1949.
3. Roughton, F. J. W., Darling, R. C., and Root, W. S.: Factors Affecting the Determination of Oxygen Capacity, Content and Pressure in Human Arterial Blood, *Am. J. Physiol.* **142**:708, 1944.
4. Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial Septal Defect. Study of Hemodynamics by the Technique of Right Heart Catheterization, *Am. J. M. Sc.* **210**:480, 1945.
5. Dexter, L. D., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E., and Evans, J. M.: Studies of Congenital Heart Disease. I. Technique of Venous Catheterization as a Diagnostic Procedure, *J. Clin. Investigation* **26**:547, 1947.
6. Bing, R. J., Vandam, L. D., and Gray, F. D.: Physiological Studies in Congenital Heart Disease. I. Procedures, *Bull. Johns Hopkins Hosp.* **80**:107, 1947.
7. Roesler, H.: Interatrial Septal Defect, *Arch. Int. Med.* **54**:339, 1934.
8. Bedford, D. E., Papp, C., and Parkinson, J.: Atrial Septal Defect, *Brit. Heart J.* **3**:37, 1941.
9. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of Blood Pressure From the Left Auricle and the Pulmonary Veins in Human Subjects With Interatrial Septal Defect, *Am. J. Physiol.* **150**:267, 1947.
10. Burchell, H. B., and Wood, E. H.: Physiologic Measurements in Cardiac Malformations, *Mod. Concepts Cardiovasc. Dis.* **17**:25, 1948.
11. Hickam, J. B., and Cargill, W. H.: Effect of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and in Patients With Cardiovascular Disease and Pulmonary Emphysema, *J. Clin. Investigation* **27**:10, 1948.
12. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease. III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect, and Auricular Septal Defect, *J. Clin. Investigation* **26**:561, 1947.
13. Stead, E. A., Jr., Hickam, J. B., and Warren, J. V.: Mechanism for Changing the Cardiac Output in Man, *Tr. A. Am. Physicians* **60**:74, 1947.
14. Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Dresdale, D.: The Influence of Short Periods of Induced Acute Anoxia Upon Pulmonary Artery Pressures in Man, *Am. J. Physiol.* **150**:315, 1947.
15. Liljestrand, G.: Regulation of Pulmonary Arterial Blood Pressure, *Arch. Int. Med.* **81**:162, 1948.
16. Aperia, A.: Hemodynamical Studies, *Skandinav. Arch. f. Physiol. Suppl.* **16** to vol. **83**:35, 1940.
17. Massee, J. C.: Atrial Septal Defect, Correlation of Autopsy Findings With Data Obtained by Right Heart Catheterization, *Am. J. M. Sc.* **214**:248, 1947.

CARDIAC DYSFUNCTION IN HYPERTHYROIDISM

A STUDY OF 810 CASES

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CARDIAC insufficiency and arrhythmias are common in hyperthyroidism. When associated with this condition, they lend themselves to permanently successful therapy more often than when found in conjunction with organic heart disease. Because cardiac insufficiency and arrhythmia can be terminated in such a high proportion of cases, further study of cardiac dysfunction in hyperthyroidism seems warranted.

The cardiovascular complications of the hypermetabolic state were first noted by Caleb Parry in 1786, as described in his unpublished writings.^{1,2} Then in the latter half of the 1830's Graves and Basedow¹ both described the association of cardiovascular symptoms and exophthalmic goiter. Similar notes are known to have been made by Stokes¹ in 1854 and Potain¹ in 1863.

In retrospect, the true cause and effect relationship of hyperthyroidism on cardiac function was made clearer by Trousseau's error¹ in 1863 when he gave tincture of iodine in place of tincture of digitalis to a patient suffering from cardiac failure. On discovering his error he stopped the iodine, whereupon the cardiac symptoms of his patient worsened. (The clinical significance of iodine was not realized until sixty years later.) In 1879 Lockridge³ proposed the term "cardiac exophthalmic goiter."

In 1896 Moebius¹ accented the importance of the involvement of the circulatory system in thyroid disease, and three years later Kraus¹ presented the toxic theory of exophthalmic goiter. Various abnormalities in the myocardial conduction system in thyrotoxicosis were shown visually by electrocardiographic tracings in 1918.⁴

The first extensive series of cases studied was in 1922,⁵ when it was observed that a large number of patients past middle life exhibited various conduction defects. In 1923 a review was published⁶ showing that partial or complete relief of cardiac failure could be achieved in a plurality of patients by thyroidectomy. In that same year the concept was propounded⁷ that the development of auricular fibrillation was dependent more on the duration than on the severity of the increased metabolic state. Other observers⁸ agreed with this concept.

Periodically since these original papers, there have been more extensive clinical studies evaluating the cardiovascular state in patients with hyperthyroidism. At times there has been controversy over the interpretation of the results, but certain basic clinical facts are agreed upon. These will be incorporated in the discussion that follows.

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From the pathologic standpoint early observers disputed the occurrence of specific myocardial lesions in those cases of hyperthyroidism with cardiovascular involvement. In 1921 Goodpasture⁹ reported two cases showing myocardial necrosis, and these clinical findings were reproduced in animal experiments.¹⁰ Other authors^{11,12} also found focal myocardial degeneration. However, the present-day concept, expressed by Hellwig,¹³ Rake,¹⁴ and Kepler and Barnes,¹⁵ is that there are no primary histologic myocardial changes resulting from hyperthyroidism.

From the physiologic standpoint, there is a common belief^{16,17,18} that the circulation of the blood is accelerated and that the cardiac output is increased to enable the transport of larger quantities of oxygen to the overactive tissues of the thyrotoxic patient. This additional burden, if untreated, will lead to cardiac insufficiency, especially in the presence of associated organic heart disease. In 1941, after careful animal experimentation, Rasmussen¹⁹ expressed a conflicting opinion: that the principal deleterious effect of the thyroid hormone on the heart and circulation is not the creation of extra work owing to the increased oxygen transport, but is its influence on cardiac rhythm. Thyroid hormone in excess, he believes, causes functional heart disease, of which the essential feature is paroxysms of tachycardia, leading to failure. From this he argues that tachycardia is not a mechanism of circulatory adjustment but is a condition in itself detrimental to the heart and circulatory system.

The roentgenographic appearance of the heart has likewise been the subject of controversy. The minority²⁰ believe that the cardiac silhouette is characteristically that of a "ham heart," due to a high aortic arch and an increased prominence of the superior vena cava and pulmonary conus. The majority^{21,22} hold that there is no physiognomic silhouette and that cardiac enlargement shows a direct relationship to age and coincident cardiovascular disease. Yet it is conceded that there may be the picture of the so-called "ham heart" in some cases uncomplicated by organic heart disease and of sufficient duration of the toxic state. Gotta²³ expresses still another viewpoint, that the prominence of the pulmonary conus is purely of constitutional origin and not the result of hyperthyroidism.

The consensus is that there are no consistent electrocardiographic patterns peculiar to thyrotoxicosis. A variety of changes in T waves and RS-T segments, as well as the presence of auricular fibrillation, auricular flutter, and both A-V and bundle branch block, have been reported.²⁴⁻²⁷ Detailed discussion is outside the province of this paper.

With this historical review in mind, a series of 810 patients with hyperthyroidism admitted to the ward and private services of St. Luke's Hospital between 1927 and 1947 were reviewed. Those with borderline signs and symptoms were excluded.

In this report patients with either persistent auricular fibrillation or signs of cardiac insufficiency on admission were classified as thyrocardiacs, whether or not there was associated organic cardiovascular disease. Those with hyperthyroidism who did not meet these standards were classified as nonthyrocardiacs and were used as controls.

Admittedly, paroxysmal tachycardia, paroxysmal fibrillation, and extrasystoles are the most common cardiac manifestations of hyperthyroidism, but the accurate evaluation of these arrhythmias in such a survey is not feasible. Moreover, they do not enter into the arbitrary criteria of the thyrocardiac.^{18,28}

ANALYSIS OF THE MATERIAL

General.—Of the 810 cases, 103 (12.5 per cent) were thyrocardiacs. Table I outlines the method of their treatment. Those cases listed in the operative column as being treated with either x-ray therapy or thiouracil received them as a definitive measure. Because symptoms were not relieved, operation followed.

TABLE I. METHOD OF TREATMENT OF 103 THYROCARDIACS

Total operative cases	72	Total nonoperative cases	31
Operation alone	62	X-ray therapy	10
X-Ray therapy followed by operation	9	Radium	1
Thiouracil followed by operation	1	Thiouracil	4
		No treatment*	16

*Includes those who died before treatment was instituted and those who refused treatment.

The seventy-two thyrocardiacs surgically treated had an operative mortality of 6.9 per cent. Six thyrocardiacs died as a result of cardiovascular complications before definitive treatment could be instituted, either operative or conservative. There were 623 nonthyrocardiacs operated upon, with a mortality of 2.2 per cent, which for the past ten years alone has been 1.4 per cent. Any death within ten days of surgery was considered an operative mortality. The greater operative risk to thyrocardiacs was also found at the Lahey Clinic,²⁹ where the figure 6.6 per cent was reported when comparable standards were used. The reason for the greater operative hazard among thyrocardiacs will become evident as the discussion develops. The incidence of carcinoma of the thyroid among the surgically treated individuals with hyperthyroidism was 0.3 per cent.

Sex Distribution.—Table II presents the data on sex distribution.

TABLE II. SEX DISTRIBUTION

	THYROCARDIAC	NONTHYROCARDIAC	TOTAL
Men	26	106	132
Women	77	601	678
Total	103	707	810

Of the 103 thyrocardiacs, 25 per cent were men, and 75 per cent women. On the other hand, among the nonthyrocardiacs there were 15 per cent men and 85 per cent women. From these figures it is seen that whereas fewer men are afflicted with hyperthyroidism, they are more likely to have cardiovascular complications.

Average Age.—The age of thyrocardiacs on admission averaged 51 years, whereas that of the nonthyrocardiacs averaged 41 years. In order to account

for the age difference between the two groups, it may be postulated that the cardiovascular system of thyrocardiacs, already impaired by the expected degenerative process of an additional ten years, is more susceptible to the toxic influence of the thyroid hormone. The age of male thyrocardiacs averaged 47 years, and of female, 54. The average age among the nonthyrocardiacs in each sex was ten years less. There is no satisfactory explanation for the fact that men in both groups are consistently younger than women.

An analysis was made which compared the age of the patients to the type of gland. It was found, both in thyrocardiac patients and nonthyrocardiac control patients, that patients of both sexes with toxic nodular glands were, on the average, approximately ten years older than those with toxic diffuse glands. An explanation of this difference may rest on a previous observation³⁰ that many of the patients with toxic adenomata have a prolonged or intermittent subclinical course. This in turn would delay diagnosis, in contradistinction to the early diagnosis of those with diffuse goiters who have a more explosive course.

Symptom Duration.—A difference was found in the median duration of toxic symptoms between thyrocardiacs (13.1 months) and controls (10.8 months). Among the thyrocardiacs there was no significant difference in symptom duration either between men and women or between types of gland, although men and patients with diffusely enlarged glands experienced slightly shorter duration of symptoms before treatment. The control group did exhibit significant difference in that men had a shorter duration of symptoms than women. Moreover, those individuals with diffusely enlarged glands were ill for a shorter period before treatment than patients with adenomatous glands.* Three thyrocardiacs did not exhibit outward evidence of thyrotoxicosis, and to them the term "masked hyperthyroidism," as used by Likoff and Levine,²⁸ is applied. In these instances the cardiac signs and symptoms overshadowed those of hyperthyroidism.

Symptoms of cardiac dysfunction in thyrocardiacs were evident for a median duration of eight months. In this group, however, individuals with toxic adenomata had noticed symptoms for twice as long as those with toxic diffuse glands. Again there was no difference in symptom duration between the sexes in relation to the type of gland. That the duration of thyrotoxicosis may play a part in the development of cardiac dysfunction is reflected by the fact that the duration of symptoms in the thyrocardiacs was significantly longer than in the controls. These findings are in agreement with other reports.³⁰⁻³²

Thyrocardiac Classification.—Among the 103 thyrocardiacs there were 44 per cent with toxic nodular glands (six men and thirty-nine women), and 56 per cent with hyperplastic glands (twenty men and thirty-eight women). In comparison, among the controls there were 34 per cent with toxic nodular glands and 66 per cent with hyperplastic glands. Although in our group of thyrocardiacs there was about equal dispersion between toxic nodular and hyperplastic glands, there has been dispute on this point in the literature,^{33,34} to the effect that the incidence of toxic nodular glands among thyrocardiacs is higher.

*In every case the frequency was broken at 11.8 months, the median of the over-all distribution.

Coexisting Cardiovascular Disease.—On the basis of clinical and laboratory investigation, 755 cases could be classified as to the presence or absence of coexisting cardiovascular disease. Of ninety-eight thyrocardiacs, 52 per cent had associated cardiovascular disease, compared with 13 per cent in the 657 controls. Clearly seen is the influence of organic disease on the production of cardiac manifestations in thyrotoxicosis. Despite the fact that the thyrocardiacs were ten years older, on an average, than the controls, the incidence of organic heart disease among them is higher than would be expected in their age group. However, attention should be called to the fact that as many as 48 per cent of thyrocardiacs had no demonstrable organic heart disease.

Types of Coexisting Cardiovascular Disease.—Table III presents the analysis of patients with coexisting cardiovascular disease. With the exception of the higher incidence of arteriosclerotic heart disease in this series, the results closely approximate the study of Likoff and Levine.²⁸

TABLE III. COEXISTING CARDIOVASCULAR DISEASE IN HYPERTHYROID PATIENTS

TYPE OF DISEASE	THYROCARDIAC		NONTHYROCARDIAC	
	CASES	PER CENT	CASES	PER CENT
Arteriosclerotic heart disease	21	42	15	18
Hypertensive cardiovascular disease	20	40	54	64
Combined arteriosclerotic and hypertensive cardiovascular disease	3	6	2	2
Rheumatic heart disease	6	12	14	16
Totals	50	100	85	100

Influence of Coexisting Cardiovascular Disease on Cardiac Insufficiency in Thyrocardiacs.—From Table IV the influence of associated cardiovascular disease on cardiac insufficiency is evident. Of those patients in failure, thirty-six had coexisting cardiovascular disease and eighteen had none demonstrable.

TABLE IV. COEXISTING CARDIOVASCULAR DISEASE AND CARDIAC INSUFFICIENCY

	PATIENTS WITH CARDIOVASCULAR DISEASE		PATIENTS WITHOUT CARDIOVASCULAR DISEASE	
No failure	14		30	
Failure	36		18	
Minimal*	20		10	
Moderate†	12		5	
Severe‡	4		3	
Totals	50		48	

*Minimal: One or more of the following: Basal râles, ankle edema, or pulmonary congestion indicated by x-ray study.

†Moderate: The status between the two extremes.

‡Severe: Orthopnea, hydrothorax, hepatomegaly, massive edema, and so forth.

When cardiac failure was considered, there were fifty-four cases of cardiac insufficiency. The distribution between sexes is interesting, because only 32 per cent of the male thyrocardiacs, compared to 60 per cent of the female thyrocardiacs, had signs of cardiac insufficiency. A greater percentage of male thyrocardiacs in failure would be expected, since in the past the greater intensity of hyperthyroidism among men in comparison to women has been generally noted.³⁵⁻³⁷ It has also been emphasized^{31,32} that the development of cardiac complications may depend on the intensity of the disease. However, in this series, the percentage of men in failure was small. Furthermore, there was no apparent difference in the severity of thyrotoxicosis, as measured by signs, symptoms, and elevated basal metabolic rate, between thyrocardiacs and non-thyrocardiacs.

Cardiac Rhythm and Failure.—Persistent auricular fibrillation on hospital admission was present in the majority of thyrocardiacs, as is shown in Table V. No significant difference between the two types of glands was found in women. In men, the small number of cases obviates comparison. Among the fifty-four patients with congestive failure, thirty-five (65 per cent) had accompanying auricular fibrillation. This figure is appreciably lower than the more than 90 per cent previously reported.³⁸ In agreement with Slesinger,³⁹ no relationship appeared between the severity of the thyrotoxicosis and development of the auricular fibrillation. Of the thirty-five patients with both congestive failure and auricular fibrillation, twenty-three had associated cardiovascular disease and twelve had none demonstrable. The greater frequency of cardiac failure in the presence of organic heart disease is consistent. In comparison, thirty-seven patients had auricular fibrillation without failure.

TABLE V. THE INCIDENCE OF AURICULAR FIBRILLATION IN THYROCARDIACS

	MEN	MEN WITH AURICULAR FIBRILLATION	WOMEN	WOMEN WITH AURICULAR FIBRILLATION	TOTAL WITH AURICULAR FIBRILLATION	PER CENT OF TOTAL WITH AURICULAR FIBRILLATION
Nodular	6	4	39	27	31	69
Diffuse	20	16	38	25	41	71
Totals	26	20	77	52	72	70

Although cardiac decompensation in the presence of normal sinus rhythm and in the absence of demonstrable independent cardiac disease is said to be a rarity,⁴⁰ ten such examples were found in this series.

Adequate postoperative data were available for thirty-six individuals who had persistent auricular fibrillation. Of these, twenty reverted to sinus rhythm—twelve within one month, six within six months, and two within eighteen months. The remaining sixteen did not revert while under observation. Twelve were observed for more than six months. Since quinidine was used in only one case, the rate of spontaneous reversion to sinus rhythm (53 per cent) was in accord with the findings of Anderson.⁴¹ However, he found that with the use of quinidine in the immediate postoperative period, reversion to normal rhythm occurred in more than 90 per cent of the patients. That reliance on spontaneous reversion should not be depended upon is also stressed by others.^{38,42}

The incidence of transitory postoperative auricular fibrillation among nonthyrocardiacs was 4.2 per cent. This figure is slightly higher than that quoted by Means.⁴³ A theory⁴⁴ to explain the cause of postoperative auricular fibrillation is that, following thyroidectomy, there is a rise in the basal metabolic rate for the first twenty-four hours, mainly as the result of fever and anxiety. One would suppose that auricular fibrillation would be a more frequent complication among nonthyrocardiac patients who had coexisting cardiovascular disease than among those without it. But in this series only 23 per cent of those with postoperative auricular fibrillation had associated cardiovascular abnormalities.

Precordial Pain.—Among thyrocardiacs there were 11 per cent who complained of angina, whereas in the controls there were only 3.5 per cent. The ratio of men to women was 3 to 1 in the former and 4 to 1 in the latter.

Electrocardiographic Study.—A total of 556 patients had electrocardiographic studies. No consistent patterns were established in either group. Compatible with their being in a higher age group and having a greater incidence of associated cardiovascular disease, thyrocardiacs appeared to have more frequent abnormalities than did the controls.

Follow-up.—Fifty-six thyrocardiacs were followed for an average of four and one-half years. Table VI shows the distribution of the follow-up.

TABLE VI. LENGTH OF THYROCARDIAC FOLLOW-UP

YEARS	NUMBER OF CASES
0-1	10
1-2	7
2-5	19
5-10	11
10-13	9
Total	56

The follow-up in Table VII shows the high proportion of excellent results in this type of heart disease. A probable explanation for the unfavorable results in the patients treated by x-ray is that their poor operative risk warranted only conservative therapy. For the same reason those patients treated with thiouracil, not shown in the table, made little improvement. Of the five so treated, four were followed, one of whom later came to operation and obtained complete relief of symptoms.

TABLE VII. RESULTS OF FOLLOW-UP OF THYROCARDIACS IN FAILURE ON ADMISSION

	OPERATIVELY TREATED	X-RAY TREATED
Patients regaining and maintaining compensation	24	1
Patients regaining and not maintaining compensation	1	0
Patients not regaining compensation	7	4
Total patients followed	32	5

Of the thirty-seven individuals with persistent auricular fibrillation and without cardiac decompensation, sixteen were followed postoperatively and showed no cardiac insufficiency during the average follow-up period of four and one-half years. In the control group, 184 patients were followed a minimum of five years. Five of these became decompensated on an average of ten years postoperatively, and one suffered a myocardial infarct after five years.

It is of some consequence that once a thyrocardiac has regained compensation following treatment, he is no more likely to suffer similar subsequent episodes than is a patient in the control group.

SUMMARY AND CONCLUSIONS

Certain important points should be reviewed to summarize the foregoing analysis and discussion. Despite the greater operative hazard among thyrocardiacs in failure, there are few other diseases leading to cardiac insufficiency that can be treated with so high an expectation of a return to normal.

In this study a group of patients with hyperthyroidism who did not exhibit either persistent auricular fibrillation or cardiac insufficiency were used as controls. Whenever possible, comparisons were drawn between them and the thyrocardiacs.

That the severity of hyperthyroidism does not play an etiological role in the production of a thyrocardiac has been illustrated. Indeed, three patients in failure in this series showed no outward evidence of hypermetabolism. The postoperative alleviation of their apparent myocardial disease is proof of the validity of this concept.

In the presence of hyperthyroidism in this series, the pathologic state of the gland, adenomatous or diffuse, could not be correlated with the development of cardiac manifestations.

The one phenomenon that may not revert to normal (with operative interference alone), in the majority of cases, is persistent auricular fibrillation. In these patients the use of quinidine postoperatively is a necessity for insuring a successful outcome.

The factors of age, sex, duration of the thyrotoxic state, and coexisting cardiovascular disease all appear to play a part in the production of an abnormal cardiac status: age, inasmuch as thyrocardiacs are, on the average, ten years older than their counterparts; sex, as men are more likely to become thyrocardiacs but less prone to develop failure; duration of symptoms, since it would seem that the longer the hyperthyroid state is allowed to proceed unchecked, the more probable becomes the development of cardiac signs and symptoms; and coexisting cardiovascular disease, which in this series is present in 52 per cent of thyrocardiacs as compared to 13 per cent of the controls. Its role as an agent in the etiology of cardiac insufficiency becomes apparent when one realizes that this condition was present in twice as many of the patients in failure as in those not in failure.

In spite of all these apparently definite causative factors, it must be stressed that in any one case, no prerequisites need be fulfilled for the development of the thyrocardiac state.

We are indebted to Dr. J. W. Fertig and Miss L. R. Elveback of the School of Public Health, Columbia University, for reviewing the statistical material in this paper.

REFERENCES

1. Ginsburg, A. M.: The Historical Development of the Present Conception of Cardiac Conditions in Exophthalmic Goiter, *Ann. Int. Med.* 5:505, 1931.
2. Phillips, J., and Anderson, J. P.: Cardiac Disturbances in Goiter, *J. A. M. A.* 89:1380, 1927.
3. Lockridge, J. E.: Graves' Disease, or Cardiac Exophthalmic Goiter, *Am. Practitioner* 9:287, 1879.
4. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goiter, *Am. J. M. Sc.* 155:175, 1918.
5. Hamilton, B. E.: Clinical Notes on Hearts in Hyperthyroidism, *Boston M. & S. J.* 86:216, 1922.
6. Hamilton, B. E.: Thyroidism Complicated by Heart Failure, *J. A. M. A.* 80:1771, 1923.
7. Williams, F. A., Boothby, W. M., and Wilson, L. B.: The Heart in Exophthalmic Goiter and Adenoma With Hyperthyroidism, *M. Clin. North America* 7:189, 1923.
8. Lahey, F. H., and Hamilton, B. E.: Thyrocardiacs: Their Diagnostic Difficulties: Their Surgical Treatment, *Surg., Gynec. & Obst.* 39:10, 1924.
9. Goodpasture, E. W.: Myocardial Necrosis in Hyperthyroidism, *J. A. M. A.* 76:1545, 1921.
10. Goodpasture, E. W.: The Influence of Thyroid Products on the Production of Myocardial Necrosis, *J. Exper. Med.* 34:407, 1921.
11. Lewis, W.: The Question of a Specific Myocardial Lesion in Hyperthyroidism (Basedow's Disease), *Am. J. Path.* 8:255, 1932.
12. Goodall, J. S., and Rogers, L.: The Nature of Thyrotoxic Myocarditis, *Lancet* 1:486, 1927.
13. Hellwig, C. A.: The Goiter Heart, *Arch. Surg.* 48:27, 1944.
14. Rake, G., and McEachern, D.: A Study of the Heart in Hyperthyroidism, *AM. HEART J.* 8:19, 1932.
15. Kepler, E. J., and Barnes, A. R.: Congestive Heart Failure and Hypertrophy in Hyperthyroidism: A Clinical and Pathological Study of 178 Fatal Cases, *AM. HEART J.* 8:102, 1932.
16. Blumgart, H., and Gargle, S.: The Adaptation of the Circulation to Hyperthyroidism and to Hypothyroidism, *J. Clin. Investigation* 6:18, 1928.
17. Burwell, C. S., Smith, W. C., and Neighbors, DeW.: The Output of the Heart in Thyrotoxicosis With a Report of a Case of Thyrotoxicosis, *Am. J. M. Sc.* 178:157, 1929.
18. Hurxthal, L. M.: The Thyrocardiac, Frank Howard Lahey Birthday Volume, Springfield, Ill., 1940, Charles C Thomas, Publisher, p. 245.
19. Rasmussen, H.: Influence of the Thyroid Hormone on Heart and Circulation, *Acta med. Scandinav. (Suppl.)* 115:1, 1941.
20. Cookson, H.: The Size and Shape of the Heart in Goitre, *Proc. Roy. Soc. Med.* 25:1517, 1932.
21. Hurxthal, L. M., Menard, O. J., and Bogan, M. E.: The Size of the Heart in Goiter, *Am. J. M. Sc.* 180:772, 1930.
22. Hawley, S. J.: A Roentgen Study of the Chest in 200 Patients With Goiter, *Am. J. Roentgenol.* 32:326, 1934.
23. Gotta, H.: Size and Shape of the Heart in Hyperthyroidism, *Arch. Int. Med.* 61:860, 1938.
24. Pardee, H. E.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, 1941, Paul B. Hoeber, Inc., p. 292.
25. Don, C. S., and Langley, G. J.: Some Aspects of the Electrocardiogram in Toxic Goiter, *Quart. J. Med.* 1:9, 1932.
26. Bernstein, S. S.: Cardiac Arrhythmias in Graves' Disease, *J. Mt. Sinai Hosp.* 1:166, 1934.
27. Digilio, V.: Reversible Bundle Branch Block in a Case of Toxic Goiter, *AM. HEART J.* 15:116, 1938.
28. Likoff, W. B., and Levine, S. A.: Thyrotoxicosis as the Sole Cause of Heart Failure, *Am. J. M. Sc.* 206:425, 1943.
29. Lahey, F. H., Hurxthal, L. M., and Driscoll, R. E.: Thyrocardiac Disease, *Ann. Surg.* 118:681, 1943.
30. Ernste, A. C.: The Cardiovascular Complications of Hyperthyroidism, *Am. J. M. Sc.* 195:248, 1938.
31. Andrus, E. C.: Heart Failure With Hyperthyroidism, *New York State J. Med.* 29:661, 1929.
32. Hurxthal, L. M.: Heart Failure and Hyperthyroidism, *AM. HEART J.* 4:103, 1928.
33. McPhedran, H.: Cardiovascular Changes in Toxic Goiter, *Canad. M. A. J.* 46:471, 1942.
34. Maher, C. C., and Sittler, W. W.: The Cardiovascular State in Thyrotoxicosis, *J. A. M. A.* 106:1546, 1936.
35. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Company, p. 412.
36. Lerman, J., and Means, J. H.: Cardiovascular Symptomatology in Exophthalmic Goiter, *AM. HEART J.* 8:55, 1932.
37. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, 1937, J. B. Lippincott Company, p. 322.

38. Hurxthal, L. M.: Auricular Fibrillation in Patients With Goiter, *Am. J. M. Sc.* **179**:507, 1930.
 39. Slesinger, G. E.: Auricular Fibrillation and the Thyroid, *Brit. M. J.* **1**:65, 1939.
 40. Haines, S. F., and Barnes, A. R.: Exophthalmic Goiter With Cardiac Decompensation and Normal Cardiac Rhythm. Case Report, *Proc. Staff. Meet., Mayo Clin.* **13**:142, 1938.
 41. Anderson, J. P.: The Incidence of Auricular Fibrillation and Results of Quinidine Therapy, *AM. HEART J.* **8**:128, 1932.
 42. Barker, P. S., Bohning, A. L., and Wilson, F. N.: Auricular Fibrillation in Graves' Disease, *AM. HEART J.* **8**:121, 1932.
 43. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, 1937, J. B. Lippincott Company, p. 449.
 44. Segal, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, *Arch. Surg.* **8**:176, 1924.
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Announcement

Dr. Jonathan C. Meakins of Montreal, Canada, has accepted the Editorship of the American Heart Journal. The Journal will continue publication under his able leadership and with the assistance of an Advisory Council and with an Editorial Board to be announced in a later issue.

THE CONUS ARTERY: A THIRD CORONARY ARTERY

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THE portion of the right ventricle in the human heart known as the area of the conus arteriosus often has a unique arterial blood supply through a vessel accessory to the two main coronary arteries. The supernumerary vessel in this region, which we have called the "conus artery," arises by a separate ostium behind the right aortic valve cusp, courses over the anterosuperior surface of the right ventricle, and terminates near the anterior interventricular groove. Significant relations were found between the anatomic variations of this coronary artery and the remainder of the coronary arterial tree and the myocardium.

LITERATURE

Supernumerary coronary arteries have been observed since the days of the early anatomists. Nevertheless, they receive little attention in most modern anatomic textbooks and are usually considered as uncommon variations of little significance.^{1,2} Spalteholz³ did not refer directly to this variation in his monograph. Grant⁴ specifically stated that "the accessory coronary arteries spring from the aortic sinuses in about 4 per cent of hearts." Although Gross⁵ also commented on their infrequency, he did mention the potential function of such vessels when occlusions develop in the main coronary arteries. Clinical treatises on coronary artery disease⁶ make scant mention of these vessels. There is no reference to them in Abbott's discussion⁷ of anomalies of the coronary arterial tree.

A few investigators have noted an especially high incidence of supplementary right coronary arteries. More than a century ago, the anatomist Richard Quain⁸ clearly showed in the first plate of his atlas a large supplementary vessel arising near the right coronary artery. Quain's plates were based upon 930 dissections, and he stated that "the arteries are represented according to their most frequent arrangement."

In 1904 Banchi⁹ injected 100 hearts through the aorta with a standard chalk mass. He reported that the first ventricular branch of the right coronary artery arose directly from the sinus of Valsalva in 33 per cent of human hearts, and found two such accessory arteries in 3 per cent of his series. Banchi stated that this vessel, which he called the "adipose artery," supplied the conus arteriosus and the superior portion of the sternocostal surface of the right ventricle.

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This study was aided by a grant from the Life Insurance Medical Research Fund.

On the basis of an injection study, Piquand¹⁰ referred to the conus artery as "l'artère graisseuse de Vieussens" and stated that it was present in one-third of human hearts.

Utilizing the simple technique of unaided dissection, Symmers¹¹ determined the number of coronary arteries in 100 consecutive human hearts without regard to the presence of pathology. He found one or more accessory coronary arteries in 38 per cent. The diameters of these supplementary vessels were small (0.5 to 2.0 mm.), and they arose from the aorta within a few millimeters of the mouth of the right coronary artery. Symmers was unable to trace them farther than 6.0 to 8.0 cm. over the anterior aspect of the right ventricle, so that he did not establish their final course and distribution.

Again, in 1922 Crainicianu¹² injected 200 human hearts with radiopaque mass and found a vessel which he called the "arteria praeinfundibularis" arising in 45 per cent of the series by a separate mouth 1.0 to 3.0 mm. in diameter. In his opinion, the origin of this vessel from the aorta was only an unimportant anatomic variation of no significance in the nutrition of the heart.

Investigations in a diverse group of animals have revealed variations in the number of coronary arteries arising directly from the aorta. Fish have two, amphibia have one, and reptiles have one or two, but all show variations in number.¹³ Among mammals the usual number is two. In the dog and pig this is relatively constant: among such animal hearts injected in our laboratory,¹⁴ only ten dog hearts among ninety, and one pig heart of seventy-nine showed an accessory right coronary artery.

The origins of the coronary arteries in primates were investigated by Chase.¹⁵ There were two coronary arteries in over one-half of the hearts of 266 rhesus monkeys: in 38 per cent of his series an accessory vessel arose from the aortic sinus by a common mouth with the right coronary; in approximately 6 per cent, a third vessel arose by a separate mouth near the right coronary ostium. Chase and De Garis¹⁶ extended these observations to include other higher primates and found twenty-three accessory arteries in the coronary trees of thirty-six hearts. In only one of these hearts was there also a supplementary coronary artery on the left. The findings in the literature and in our series are tabulated below (Table I).

TABLE I. INCIDENCE OF CONUS ARTERY

ANIMAL	NUMBER OF HEARTS STUDIED	HEARTS WITH CONUS ARTERY		REFERENCE
		NUMBER	PER CENT	
Dog	90	10	11	Schlesinger ¹⁴
Pig	79	1	1	Schlesinger ¹⁴
Rhesus monkey	266	17	6	Chase ¹⁵
Higher primates	36	23	65	Chase and De Garis ¹⁶
Man	100	33	33	Banchi ⁹
		—	33	Piquand ¹⁰
	100	38	38	Symmers ¹¹
	200	—	45	Crainicianu ¹²
	651	332	51	Present series

METHOD AND MATERIALS

The human hearts on which our observations are based were all prepared by the method of injection plus dissection previously reported.¹⁷ Briefly, this consists of (1) injecting a radiopaque lead-agar mass of different colors into the two main coronary arteries, (2) unrolling the heart so that its entire arterial tree lies in one plane, (3) taking a roentgenogram of the unrolled heart, and (4) carefully dissecting the coronary arteries, using the film as a guide. This technique discloses the narrowings, occlusions, and anastomoses in the visualized coronary arteries in every heart. The conus artery attracted our attention in routine injections by this method, when the injection mass occasionally filled the conus artery by anastomotic pathways and leaked through its mouth into the aorta. Of a total series of 1,000 hearts, only 651 were used in the present analysis. The others were rejected because the observations on the conus artery were incomplete.

OBSERVATIONS

1. *Anatomy of Conus Artery.*—The conus artery, a supernumerary to the right coronary artery, arises by a separate ostium in the aorta and sends branches to the area of the conus arteriosus. It courses in the epicardium over the anterosuperior aspect of the right ventricle and terminates in small arterial twigs near the anterior interventricular groove. The film of the unrolled heart (Fig. 1) shows the close proximity of the branches of the conus artery to the branches of the left descending coronary artery. The conus artery usually arises close to the ostium of the right coronary artery, behind the same semi-lunar aortic cusp. The vessel varies considerably in size; although usually small (0.4 to 1.0 mm. in internal diameter at its origin), it may reach a diameter of 2.0 mm. or more (Fig. 2).

When the conus artery is not present, the area of the conus arteriosus is supplied by the first ventricular branch of the right coronary artery (Fig. 3). This first branch of the right coronary artery, in all respects similar to the conus artery except for its point of origin, was also given special study for purposes of comparison.

2. *Incidence of Conus Artery.*—In one-half of the 651 human hearts, single or multiple conus arteries were present (Table II). The occurrence of conus arteries is unrelated to age or sex (Table III, A and B).

TABLE II. ORIGIN OF ARTERY TO CONUS ARTERIOSUS (651 HEARTS)

	NUMBER OF HEARTS		PERCENTAGE	
Conus Artery	332		51	
Single aortic mouth		319		49
Multiple aortic mouths		13		2
First ventricular branch of right coronary artery	319		49	

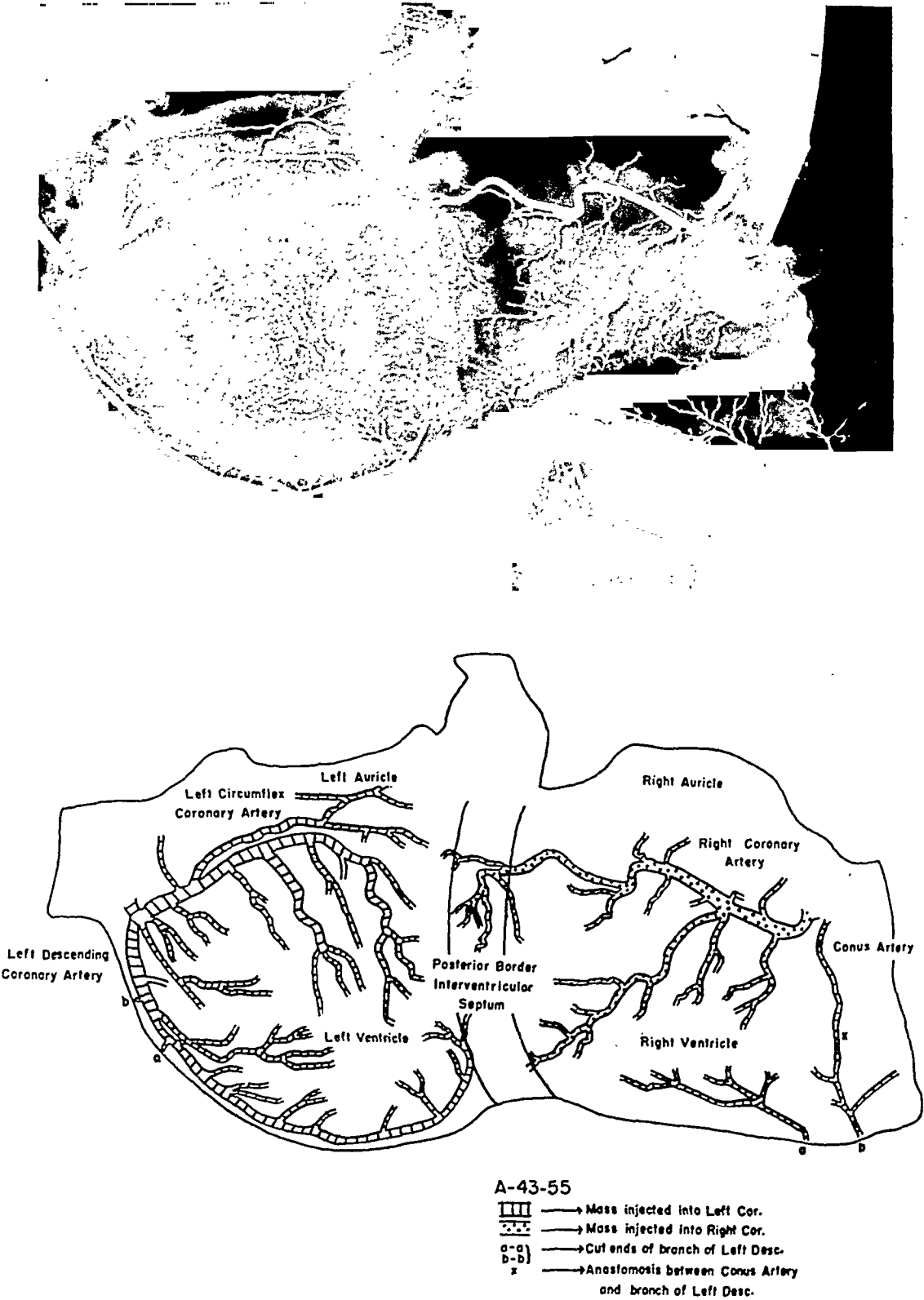


Fig. 1.—X-ray and diagram of injected normal heart showing conus artery in relation to other coronary arteries.

Case A43-55. A 59-year-old man, without evidence of hypertension, angina pectoris, or congestive failure, who died from carcinoma of the lung. Heart weight, 308 grams. No hypertrophy, valvular disease, coronary artery narrowing, or myocardial fibrosis was found. Anastomosis of the left descending coronary artery with the conus artery was present.



Fig. 2.—X-ray and diagram of injected normal heart showing large conus artery cannulated and injected with mass.

Case A42-83. A 56-year-old man without hypertension, angina pectoris, or congestive failure who died from carcinoma of the colon. Heart weight, 330 grams. No hypertrophy, valvular disease, coronary arterial narrowing, myocardial fibrosis, or anastomoses were found.

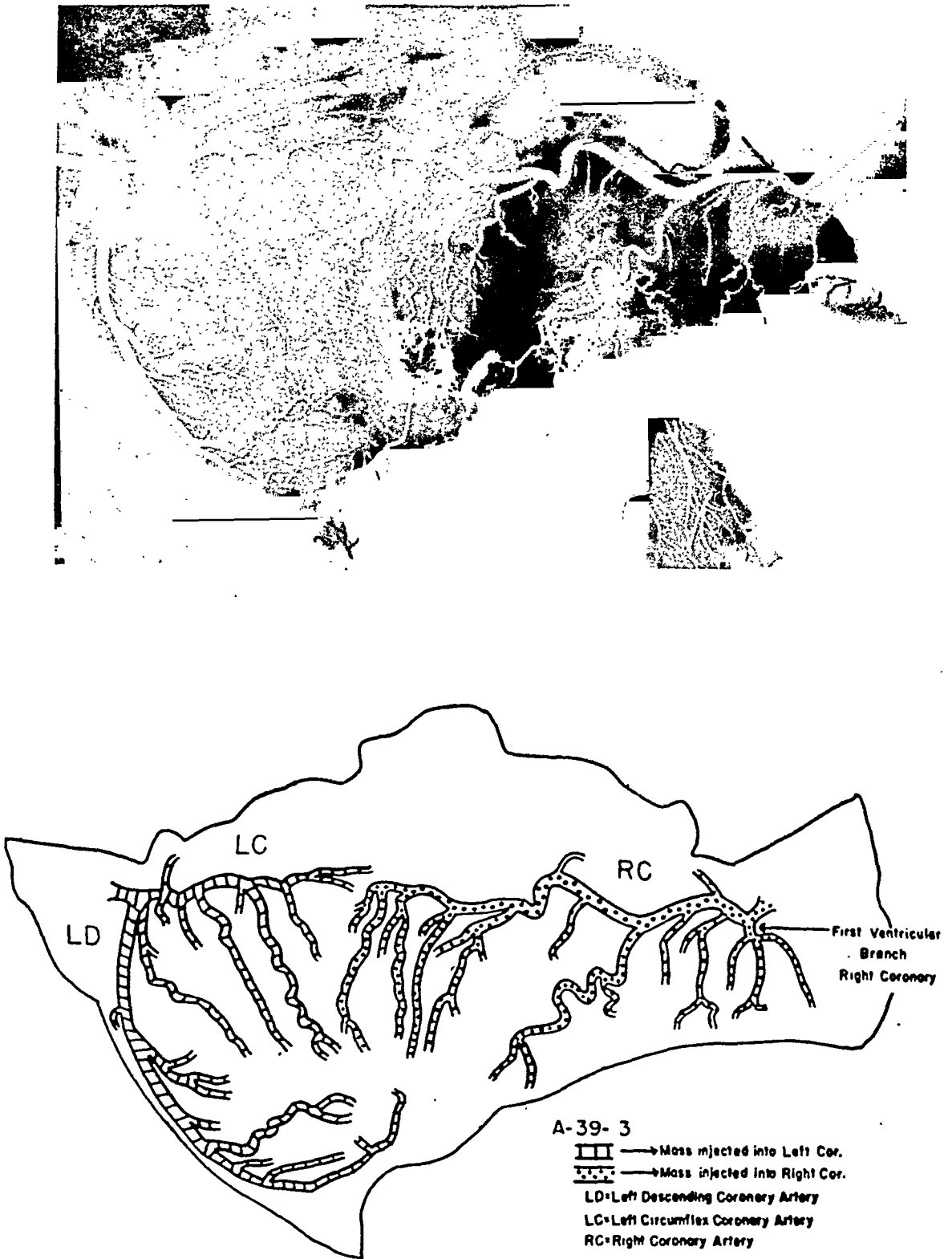


Fig. 3.—X-ray and diagram of injected normal heart showing area of conus arteriosus supplied by homologue of conus artery, the first ventricular branch of the right coronary artery.

Case A39-3. A 56-year-old man, who died from lobar pneumonia. No hypertension, angina pectoris, or congestive failure was present. Heart weight, 250 grams. No hypertrophy, valvular disease, coronary artery narrowing, myocardial fibrosis, or anastomoses were found.

TABLE III, A. ORIGIN OF ARTERY TO CONUS ARTERIOSUS IN RELATION TO AGE

AGE IN YEARS	NUMBER OF HEARTS				
	0-19	20-39	40-59	60-	TOTAL
Conus artery	11 (46%)	48 (59%)	118 (50%)	155 (50%)	332 (51%)
First ventricular branch right coronary artery	13	33	117	156	319
Totals	24	81	235	311	651

TABLE III, B. ORIGIN OF ARTERY TO CONUS ARTERIOSUS IN RELATION TO SEX

	NUMBER OF HEARTS	
	MEN	WOMEN
Conus artery	207 (53%)	125 (48%)
First ventricular branch right coronary artery	185	134
Totals	392	259

The high incidence of supernumerary conus arteries on the right is in marked contrast to the rare occurrence of vessels accessory to the left coronary artery system. The length of the common left coronary artery trunk, however, is quite variable; indeed, it is occasionally so short that the left descending and left circumflex coronary arteries arise from a common ostium in the aorta. In only four instances in the 1,000 injected hearts was the common left coronary artery stem absent completely, so that the left descending and left circumflex coronary arteries arose by separate mouths from the aorta. In two of these four hearts, the separate left circumflex coronary ostium was misplaced, arising from the aorta behind the same cusp as the right coronary artery. Complete separation of the mouths of the two left coronary arteries is apparently a major congenital anomaly.

3. *Occlusions in the Conus Artery.*—In a previous communication based on 400 hearts,¹⁸ the incidence and localization of occlusions in the main coronary arteries and their branches were reported. Detailed study of the occlusions in the branches of the coronary arteries was deferred, however, pending the accumulation of a larger series, because the variability in the number, origin, and distribution of such branches makes difficult any generalizations about them.

The conus artery and its homologue, the first ventricular branch of the right coronary, are distinct, have a relatively constant distribution, and differ only in origin. They lend themselves, therefore, to a comparative study of

the incidence of occlusions in two constant vessels of the coronary arterial tree. In the 651 hearts studied, occlusions were found in only six (1.8 per cent) of the 332 conus arteries and in five (1.6 per cent) of the 319 homologous right coronary arterial branches (Table IV). The incidence of occlusions in the conus artery and its homologue was compared with the incidence in the first branch of the left descending (2.0 per cent) and of the left circumflex (0.9 per cent) coronary arteries (Table V). In addition, all the "primary branches"* of the left descending and left circumflex coronary arteries were studied in the same way. All primary branches which measured over 1.0 mm. in diameter on the roentgenograms of the injected hearts were counted, and the incidence of occlusions in them was determined. In 976 hearts in which adequate data of this nature were available, ninety occlusions (1.5 per cent) were present in the 5,846 primary branches of the left descending coronary artery and seventy-two occlusions (1.5 per cent) were found in the 4,880 primary branches of the left circumflex coronary artery.

TABLE IV. INCIDENCE OF OCCLUSIONS IN CONUS ARTERY AND IN FIRST VENTRICULAR BRANCH OF RIGHT CORONARY ARTERY

VESSEL	NO. OF VESSELS	NO. OF OCCLUSIONS	PER CENT OF VESSELS WITH OCCLUSIONS
Conus artery	332	6	1.8
First ventricular branch right coronary artery	319	5	1.6

TABLE V. INCIDENCE OF OCCLUSIONS IN BRANCHES OF LEFT DESCENDING AND LEFT CIRCUMFLEX CORONARY ARTERIES

VESSEL	NO. OF VESSELS	NO. OF OCCLUSIONS	PER CENT OF VESSELS WITH OCCLUSIONS
First branch of left descending artery	976	20	2.0
First branch of left circumflex artery	976	9	0.9
All branches of left descending artery	5,846	90	1.5
All branches of left circumflex artery	4,880	72	1.5

The incidence of occlusions is of the same order of magnitude in the conus artery (1.8 per cent); in the first branches of the left descending (2.0 per cent), left circumflex (0.9 per cent), and right coronary (1.6 per cent) arteries; and in all other primary branches (1.5 per cent). The incidence of occlusions in all the primary branches is much less than that previously reported¹⁸ in the main coronary arteries, and is one quarter of that in the first 4.0 cm. of the main stems of the coronary arteries, and one half of that in the distal segments of the main stems.

*By "primary branch" is meant any artery arising directly from the left descending, left circumflex, or right coronary artery.

4. *Anastomoses With Conus Artery.*—In this series, anastomotic communications between coronary arteries are demonstrated either by the injection of a vessel distal to a complete occlusion or by a mixture of colors in nonoccluded vessels. The distribution of colors permits identification of the source of the injected mass and the pathways of anastomoses. Nondissectible, submacroscopic anastomoses between two primary branches of a nonoccluded artery are not noticed by this method, since they are filled with mass of the same color. Therefore, in hearts without occlusions, anastomoses between the first ventricular branch of the right coronary artery and the remainder of the right coronary artery would not be detected.

On the other hand, full information regarding anastomoses to the conus artery is obtainable because this artery has a separate uncannulated mouth in the aorta. Anastomotic connections between conus arteries and the injected coronary arterial tree are completely demonstrated whether or not the conus artery is occluded, for it can be filled with mass only by way of anastomotic pathways. The conus artery is strategically placed between the branches of the left descending coronary artery and the right coronary artery. It is a potential path of anastomosis to either of these major vessels. The conus artery thus offers a unique opportunity for a complete study of anastomotic filling of a single coronary vessel.

Anastomotic filling of the conus artery was observed in 123 of the 332 hearts with conus arteries. No correlation was found between the age of the patient and the incidence of anastomosis with this vessel (Table VI).

TABLE VI. INCIDENCE OF ANASTOMOSES WITH CONUS ARTERY IN RELATION TO AGE

AGE IN YEARS	NUMBER OF HEARTS				
	0-19	20-39	40-59	60-	TOTAL
Nonanastomotic conus artery	8	31	70	100	209
Anastomotic conus artery	3 (22%)	17 (35%)	48 (41%)	55 (35%)	123 (37%)
Totals	11	48	118	155	332

From the 332 hearts with conus arteries, there was selected a group of 141 hearts which did not exhibit narrowings or occlusions of the coronary arteries, or any valvular disease. Hearts with hypertrophy were not excluded from this selected "control group." Anastomotic filling was found in the conus arteries of thirty-one (22 per cent) of these 140 selected control hearts (Table VII). In the same group of control hearts, twenty-six (18 per cent) showed interarterial anastomoses with vessels other than the conus artery. Although these figures are statistically similar, the incidence of anastomoses in conus arteries is signifi

cant, because the remainder of the coronary arterial tree presents several times as large a potential bed for anastomoses as that surrounding the conus artery.

TABLE VII. RELATION OF CONUS ARTERY ANASTOMOSES TO CORONARY ARTERY OCCLUSION

	141 HEARTS WITHOUT CORONARY ARTERY NARROWING, OCCLUSION, OR VALVULAR DISEASE		71 HEARTS WITH OLD OCCLUSION	
	NO. OF HEARTS	PER CENT	NO. OF HEARTS	PER CENT
Anastomoses with conus artery	31	22	43	61
Anastomoses elsewhere in entire coronary arterial tree	26	18	70	100

The potentialities of the conus artery as a source of anastomotic blood supply to the myocardium are more fully displayed in the hearts with old coronary artery occlusions. Among the 332 injected hearts with conus arteries, there were seventy-one with old occlusions in vessels other than the conus artery. There was anastomotic filling of forty-three (61 per cent) of the conus arteries of these hearts (Table VII). In keeping with previous observations,¹⁸ almost universal (99 per cent) anastomotic filling was found in vessels distal to old occlusions (Table VII).

Thus, there was an increase in the incidence of anastomoses involving the conus artery, from 22 per cent in hearts without coronary artery or valvular disease to 61 per cent in hearts with old coronary artery occlusions. Occlusions anywhere in the coronary arterial system appear to stimulate anastomotic channels between the conus vessel, which receives blood directly from the aorta, and other coronary artery branches not so situated.

ILLUSTRATIVE CASES

Indeed, in individual hearts it was often obvious that conus arteries were important anastomotic channels for the transport of blood directly from the aorta to a portion of the coronary arterial tree distal to an occlusion. The value of such anastomotic connections depends upon their number and caliber, the size of the conus artery, and also upon the location of the anastomosis in relation to the narrowings or occlusions. The following two cases serve to illustrate these potentialities of the conus artery.

CASE 1 (A42-85).—Fig. 4 represents a heart in which the conus artery was a major source of blood supply to the other coronary arteries distal to occlusions within them. This patient had had angina pectoris for three years, without clinical evidence of myocardial infarction. Although five old occlusions were found in the three main coronary arteries, there was no old or fresh infarction in this heart. During life a considerable portion of the blood supply to the myocardium was probably derived from the unobstructed conus artery. This vessel, of appreciable size, helped prevent myocardial infarction by supplying blood through a series of anastomotic pathways.

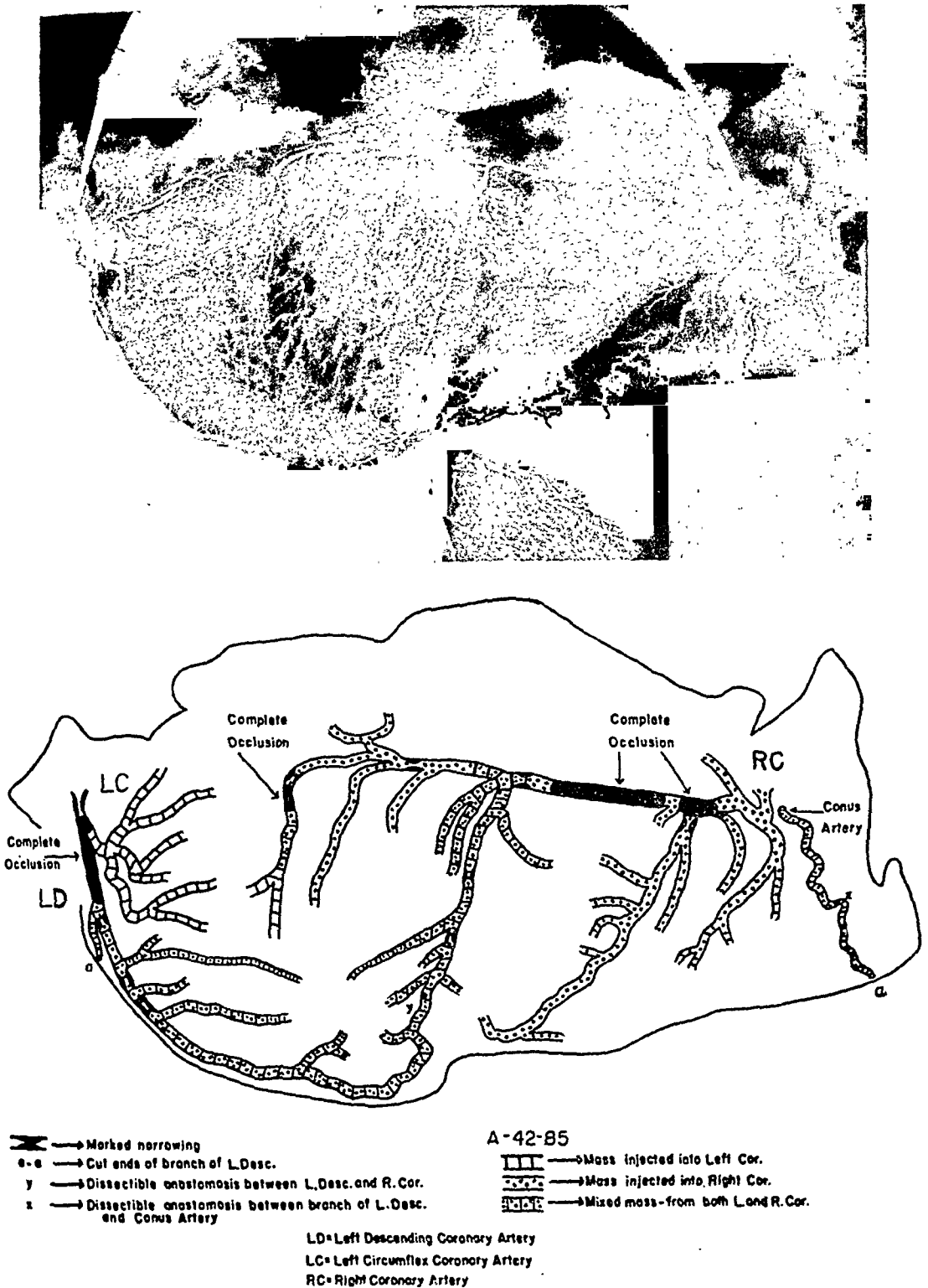


Fig. 4.—X-ray and diagram of injected heart showing occlusions in all main coronary arteries, with anastomosis between branch of left descending and conus arteries.

Case A42-85. A 60-year-old hypertensive man, whose death from pyelitis was preceded for three years by angina pectoris and exertional dyspnea. Heart weight, 500 grams. Left ventricular hypertrophy. Five old occlusions in left descending, left circumflex, and right coronary arteries. Moderate myocardial fibrosis without myocardial infarction. Extensive anastomosis between left descending and right coronary arteries, as well as large, grossly dissectible anastomosis between conus artery and branch of left descending artery distal to an occlusion in the latter.

CASE 2 (A46-60).—Fig. 5 represents a heart with congenital pulmonic stenosis in which the conus artery and the left descending coronary artery together brought a real, though perhaps insignificant, amount of aortic blood to the pulmonary artery distal to the stenosis. The anastomotic circulation in this heart presents a spontaneous systemic-pulmonic shunt analogous to those now being produced surgically for the treatment of pulmonic stenosis.

DISCUSSION

The artery to the conus arteriosus (conus artery), arising directly from the aorta by an independent ostium in 50 per cent of human hearts, has not received the attention it deserves. Although study of this vessel by ordinary dissection is comparatively easy, it is facilitated by the use of an injection method. Thus, there are obtained, in a variety of hearts, additional data which would not be available without such a technique. This method, which was especially devised for studying arterial occlusions, disclosed an incidence of occlusions in the conus artery similar to that in the primary branches of the coronary arterial tree. Although the conus artery arises directly from the aorta, it does not have the high incidence of occlusions found in the first 4 cm. of the coronary artery trunks. Our observations, therefore, lend no support to the concept that the higher incidence of occlusions near the ostia of the main coronary arteries is, in some way, related to the presumably higher blood pressure in this portion of these vessels.

Since the conus artery receives blood directly from the aorta, it differs markedly as a potential collateral source of blood supply from its homologue, the first ventricular branch of the right coronary artery. Because of its separate origin, the conus artery is independent of obstruction so often found at or near the mouth of the right coronary artery, and affecting its first ventricular branch.¹⁸ By the special features which distinguish it from the rest of the coronary arterial tree, the conus artery appears particularly suited as a collateral source of blood supply. Its direct communication with the aorta and its location between the main left descending and the right coronary arteries make it a ready source of anastomotic connection between the aorta and the coronary arterial tree distal to the zones in which the incidence of occlusions is highest. Furthermore, the low incidence of occlusions in the conus artery, lower than in any other coronary artery directly connected with the aorta, enhances its value as an effective pathway of collateral blood supply. In the presence of old occlusions anywhere in the heart, the incidence of anastomoses with the conus artery increases threefold. This unique vessel responds to the need for increased blood supply as if it were an accessory artery strategically placed between the left descending and right coronary arteries, which supply most of the blood in most human hearts. It appears that the clinical consequences of occlusion in these two coronary arteries may be significantly influenced by the presence or absence of a conus artery.

The existence of this supernumerary coronary artery, with potential anastomosis to the other coronary vessels, has not always been considered in experiments on coronary flow. In such experiments, its presence or absence should be specifically determined, and methods should be specifically devised for pre-

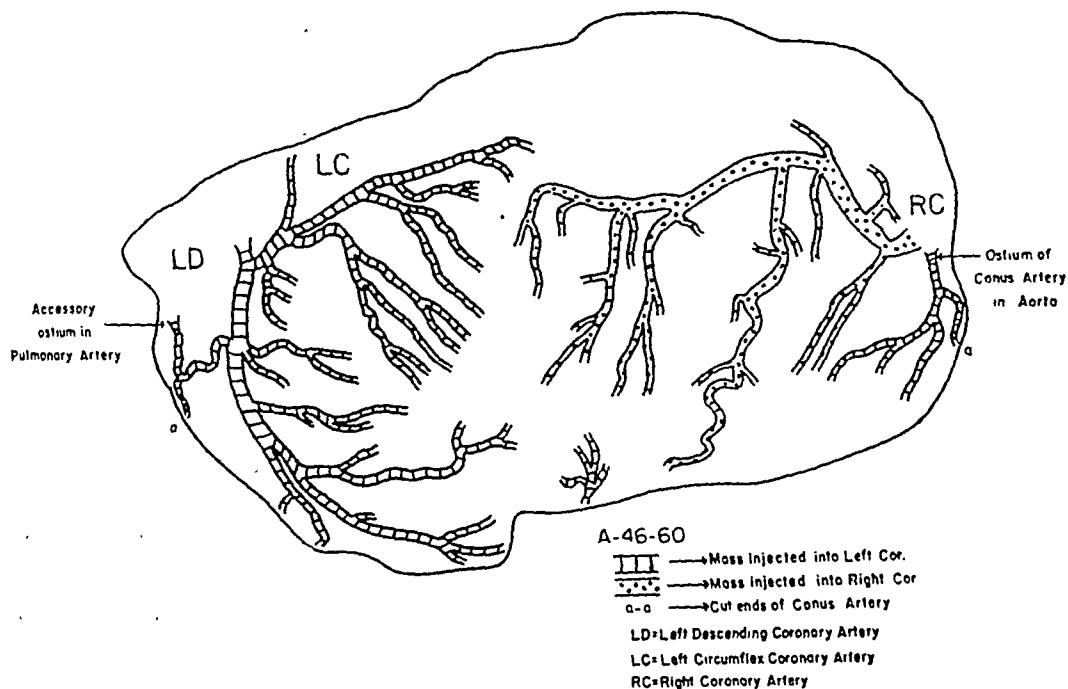


Fig. 5.—X-ray and diagram of injected heart with pulmonic stenosis, showing anastomosis between aorta and pulmonary artery via left descending coronary and conus arteries.

Case 46-60. A 49-year-old woman, who died of chronic leucemia. Enlarged heart with a pulmonic systolic murmur and thrill. No hypertension, angina pectoris, or congestive failure was noted. Heart weight, 445 grams. Right ventricular hypertrophy; interauricular septal defect; congenital, quadri-cuspid pulmonic stenosis. No coronary artery narrowing or myocardial fibrosis. Grossly dissectible anastomosis between the conus artery and the left descending coronary artery, with additional mouth in pulmonary artery distal to the pulmonic stenosis.

venting flow through this vessel from irrigating the coronary tree or from being confused with flow from the chambers of the heart.

CONCLUSIONS

1. In 50 per cent of the 651 human hearts studied, the conus arteriosus is normally supplied by an artery, the conus artery, which is not a branch of the right or left coronary artery, but arises directly from the aorta.

2. The incidence of occlusions in the conus artery is much lower than in the three main coronary artery trunks, but is similar to that in the primary branches of the coronary arterial tree.

3. The conus artery often serves as a source of anastomotic blood supply directly from the aorta to the other vessels of the heart when these are narrowed or occluded.

4. The amount of myocardial damage resulting from coronary artery occlusion and narrowing is in part determined by the presence or absence of anastomoses between the conus artery and the rest of the coronary arterial tree.

REFERENCES

1. Gray, H.: *Anatomy of the Human Body*, ed. 24, Philadelphia, 1942, Lea & Febiger, p. 549.
2. Cunningham's *Textbook of Anatomy*, ed. 8, New York, 1943, Oxford University Press, p. 1207.
3. Spalteholz, W.: *Die Arterien der Herzwand*, Leipzig, 1924, S. Hirzel.
4. Grant, J. C. B.: *A Method of Anatomy*, ed. 3, Baltimore, 1944, Williams & Wilkins Company, p. 520.
5. Gross, L.: *The Blood Supply to the Heart*, New York, 1921, Paul B. Hoeber, Inc., p. 30.
6. Wearn, J. T.: "The Anatomy of the Coronary Vessels," In: Levy, R. L.: *Diseases of the Coronary Arteries and Cardiac Pain*, New York, 1936, The Macmillan Company, pp. 33-34.
7. Abbott, M. E.: *Congenital Heart Disease*, Nelson Loose-Leaf Medicine 4:260, 1932.
8. Quain, R.: *Anatomy of the Arteries (Atlas)*, Plate I, London, 1844, Taylor & Walton.
9. Banchi, A.: *Morfologia delle arteriae coronariae cordis*, Arch. ital. di anat. e di embriol. 3:87, 1904.
10. Piquand, G.: *Recherches sur l'Anatomie des Vaisseaux Sanguins du Cour*, J. de l'Anat. et de la Physiol. 46:310, 1910.
11. Symmers, W. St. Clair: *Note on Accessory Coronary Arteries*, J. Anat. & Physiol. 41:141, 1907.
12. Crainicianu, A.: *Anatomische Studien über die Coronararterien und Experimentelle Untersuchungen über Ihre Durchlässigkeit*, Virchow's Arch. f. Path. Anat. 238:1, 1922.
13. Grant, R. T., and Regnier, M.: *The Comparative Anatomy of the Cardiac Coronary Arteries*, Heart 13:285, 1926.
14. Schlesinger, M. J., and Zoll, P. M.: Unpublished data.
15. Chase, R. E.: *The Coronary Arteries in 266 Hearts of Rhesus Monkey*, Am. J. Phys. Anthropol. 23:299, 1938.
16. Chase, R. E., and De Garis, C. F.: *Arteriae Coronariae (Cordis) in the Higher Primates*, Am. J. Phys. Anthropol. 24:427, 1939.
17. Schlesinger, M. J.: *An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses*, AM. HEART J. 15:528, 1938.
18. Schlesinger, M. J., and Zoll, P. M.: *Incidence and Localization of Coronary Artery Occlusions*, Arch. Path. 32:178, 1941.

VI. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN POSTEROLATERAL INFARCTION

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WILSON and co-workers^{1,2} have drawn attention to the electrocardiographic findings in posterolateral infarction, as distinguished from plain posterior and high lateral infarction. Their descriptions cover the classical findings in the standard leads and in unipolar thoracic, esophageal, and limb leads. Typical cases are manifested by abnormal Q_2T_2 and Q_3T_3 patterns due to the posterior lesion, accompanied by a small Q_1 and inverted T_1 due to the lateral lesion.^{1,2,3} However, even the full pattern in the standard leads cannot be regarded as pathognomonic of posterolateral infarction, since it may be duplicated by antero-posterior infarction⁴ and perhaps by anterolateral infarction when the heart is in vertical position.^{1,5}

Valuable additional information would be expected from the use of multiple unipolar leads, since Leads V_5 , V_6 , and aV_L reveal many lateral lesions not diagnosable from Lead I,^{1,2,6} whereas Lead aV_F provides a more reliable index of the posterior lesion than do Leads II and III.^{7,8} The typical findings, as set forth by the Wilson group,^{1,2} are: (1) abnormal Q waves in the unipolar leads from the left leg and the ventricular levels of the esophagus; (2) diagnostic QT patterns in Lead V_6 and perhaps in Lead V_5 , as well; and (3) reciprocal changes in leads from the right side of the precordium, consisting of early depression of the RS-T segment and subsequent exaggeration of the R and T waves.

No data are available as to the accuracy which may be attained in the detection and localization of posterolateral infarcts through the use of multiple unipolar leads, since the Wilson group has had little opportunity to follow their patients to autopsy, whereas other workers have not given consideration to posterolateral infarction as a separate entity. Therefore, an analysis will be presented of the electrocardiographic findings in our group of thirty-three patients with pathologic evidence of infarction of the posterolateral wall of the left ventricle. Fourteen of these will be presented in detail; eleven others were reported previously⁸; and the eight remaining will appear in a succeeding manuscript on primary lateral infarction.⁹ The findings pertaining to the lesion of the posterolateral wall will be summarized for all cases.

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CASE REPORTS

CASE 124.—A 55-year-old diabetic woman gave a classical history of angina pectoris, beginning in January, 1945. The first prolonged attack of retrosternal constriction occurred on Dec. 25, 1945, and a second began on Jan. 13, 1946, leading to admission to the hospital the following day. In spite of strict bed rest, there were many recurrences of retrosternal pain, generally relieved by nitroglycerine. On February 19 a much more severe attack occurred, complicated by circulatory collapse. Blood pressure remained at shock levels until her death on February 25. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 1 include a tracing on March 6, 1945, approximately two months after the onset of the angina pectoris; a tracing on Jan. 15, 1946, twenty-four hours after admission; and a third on Feb. 19, 1946, two hours after the onset of the recurrent attack, which was complicated by shock and ended in death. The standard and precordial leads of the first tracing were considered within normal limits. Lead aV_L displayed a low upright P wave and a Q wave 1.0 mm. in depth and approximately 20 per cent of the amplitude of the succeeding slurred R wave. The RS-T junction was isoelectric, but the T wave was diphasic. This pattern could be within normal limits if transmitted from the

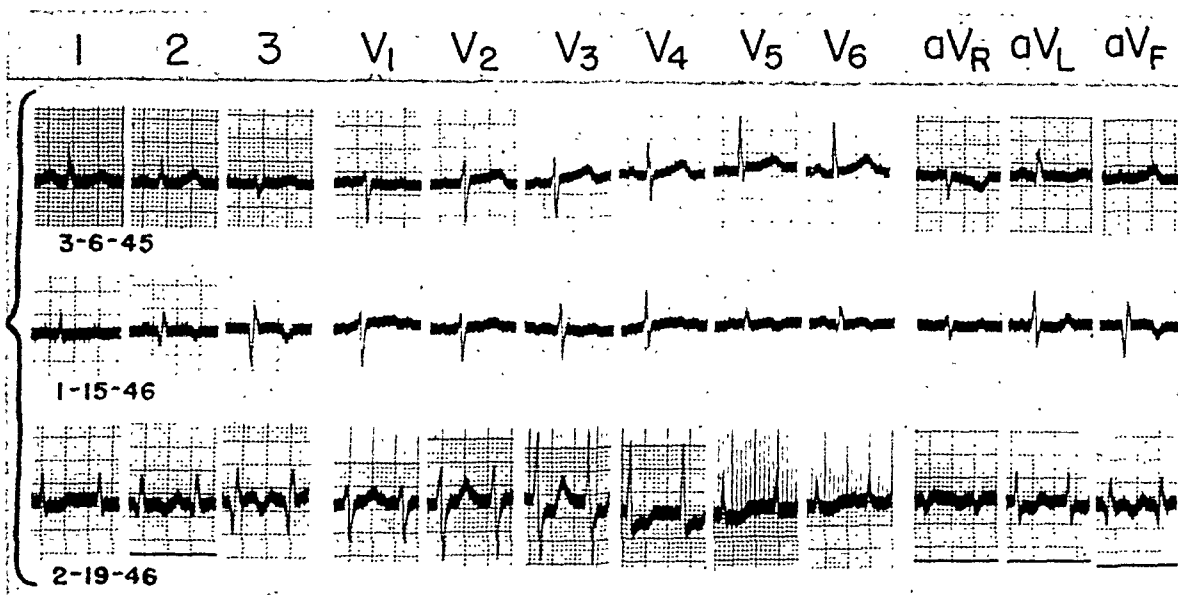


Fig. 1.—Electrocardiograms in Case 124 before and after the development of a posterolateral infarction.

posterobasal aspect of the left ventricle, but would have been abnormal if derived from the anterolateral wall of the left ventricle. In the latter event, such a finding could have been the result of left ventricular hypertrophy or of a small subendocardial lateral infarct. High precordial and axillary leads were indicated to settle the diagnosis, but unfortunately were not obtained because the patient did not return for observation in the outpatient department. The small, splintered R wave in Lead aV_F on March 6, 1945, was within normal limits. On Jan. 15, 1946, this was replaced by an abnormal QR complex and a cove-shaped inversion of the T wave typical of recent posterior infarction. The QRS complex in the first four precordial leads was almost identical with that recorded ten months previously, but the QRS complex in Leads V_5 and V_6 showed a significant change, characterized by the appearance of a Q wave and by a 66 per cent reduction in the voltage of the R wave. The QR complexes of Leads V_5 and V_6 were abnormal and, along with the bowing of the RS-T segment and inversion of the T wave, indicated continuation of the posterior infarct into the lateral aspect of the left ventricle. The standard leads were typical of posterior infarction, but failed to show the lateral extension. This was apparently due to reference of the potential variations of the uninfarcted antero-septal wall of the left ventricle to the left arm, as indicated by

the similarity in the QRS complexes of Leads V_4 and aV_L . In serial tracings during the next month, the main change consisted in a doubling of the amplitude of the R wave in Leads V_1 through V_3 , coupled with an increase in the height of the T wave in these leads to 4.0 to 5.0 millimeters. This was considered reciprocal to the organization of a posterolateral infarct. Comparison of the tracing of February 19 with the one taken the preceding day showed no significant change in the QRS pattern in any lead. The RS-T segment in Leads aV_F , II, and III showed increased upward bowing. The RS-T junction, which had been isoelectric in the precordial leads and in aV_L , became acutely depressed in Leads V_3 , V_4 , and aV_L and slightly depressed in Leads V_5 and V_6 . Two alternative explanations were considered for the RS-T depression; namely, extension of the infarct subendocardially into the anterolateral wall of the left ventricle, and a reciprocal effect from reinfarction of the posteroseptal wall. The latter was favored because of the increased upward bowing of the RS-T segment in Lead aV_F .



Fig. 2.—Roentgenogram of the injected heart in Case 124, showing an organizing posterolateral infarction in broken outline and a terminal posteroseptal and right ventricular infarct in solid lines.

Pathologic Findings.—The heart weighed 282 grams and exhibited an organizing transmural infarct of the entire posterior wall, as demarcated by the broken lines of Fig. 2. This infarct readily explained the abnormal QR pattern of Leads aV_F , II, and III on January 15. It extended into the posterolateral wall sufficiently to account for the abnormal QR pattern in Lead V_6 and the reciprocal increase in the upright deflections in Leads V_1 through V_3 , but did not extend far enough forward to explain satisfactorily the findings in Lead V_5 . Counterclockwise rotation or anterior displacement of the apex may have accounted for the transmission of the potential variations of the infarcted area to the anterior axillary line. There was microscopic evidence of recent reinfarction of the posterior wall of the left ventricle at its junction with the inter-ventricular septum, together with an infarct of one week's duration in the apex of the right ventricle, as demarcated by the solid lines of Fig. 2. A large mural thrombus filled the entire apex

of the right ventricle. The anterior and anterolateral walls of the left ventricle were intact. Therefore, the acute RS-T depression in Leads V_3 through V_6 and in aV_L on February 19 represented a reciprocal manifestation of the extension into the posteroseptal wall of the left ventricle and/or the right ventricular infarct. Because of the absence of direct evidence of the latter in right ventricular Leads V_1 and V_2 , it is probable that the reciprocal changes in left ventricular leads were referable exclusively to the extension into the posteroseptal wall of the left ventricle. The similarity of the QRS-T pattern in Leads V_1 and V_2 on February 19 to that in the same leads taken on the preceding day suggested that the right ventricular portion of the infarct may have developed after the tracing of February 19 had been taken. It is regrettable that no further electrocardiograms were obtained.

CASE 125.—A 50-year-old woman had had diabetes mellitus for twenty years, but was otherwise in good health until January, 1945, when she began to have transient attacks of retrosternal oppression, precipitated by exercise and relieved promptly by rest. Following the removal of a nontoxic thyroid adenoma in March, 1946, the angina disappeared for three months and then recurred with increasing severity. On Dec. 29, 1946, she was seized with a much more severe retrosternal pain, which continued unabated during the twenty-two hours intervening before hospitalization. She was admitted in profound circulatory collapse and died six hours later. No cardiac glycosides were administered.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 3 were taken at intervals during observation in the outpatient department and on the final admission five hours before death. The initial phase of the QRS complex was upright in the three precordial leads available on Jan. 25, 1945. The R wave in Lead V_2 was unusually small, but a positive decision between a normal variant and an abnormality could not be made in the absence of tracings from precordial Positions 1 and 3. The striking feature of this tracing was the deep cove inversion of the T waves in Leads V_2 and V_4 . This pattern brought up the following possibilities: acute antero-septal ischemia, a small intramural or subepicardial antero-septal infarct, acute right ventricular dilatation, and pericarditis. Acute right ventricular dilatation was unlikely because the T-wave inversion in transitional Lead V_4 was as great as that in Lead V_2 , and pericarditis was unlikely because of the absence of T-wave changes in Lead V_6 and in the standard leads. In the next two tracings, the T waves were tall, upright, and sharply peaked, but the QRS complex showed no significant change other than a slight variation in Leads V_3 and V_4 due to shifting in the transitional zone. The reversal in the T waves of Leads V_2 and V_4 without significant change in the QRS complex was in keeping either with the disappearance of acute antero-septal ischemia or the healing of a small intramural antero-septal infarct.¹⁰ In comparison of the QRS pattern on Dec. 30, 1946, with that in previous tracings, it was noted that a significant Q wave had appeared in Lead aV_L , but not in any other lead. An abnormal slurring or notching had developed in the terminal portion of the QRS complex of most leads, affecting the R wave in Leads V_5 , V_6 , and aV_F and the S wave in Leads V_1 through V_3 . This distribution suggested that the slurring or notching was due to a lesion in the last portion of the heart to become activated, namely, the posterobasal wall of the left ventricle. The most striking changes had occurred in the RST-T complex and consisted of abnormal elevation of the junction in Leads aV_F , II, and III and abnormal depression in Leads V_1 through V_4 and in Lead aV_L . The T waves had increased in amplitude in precordial leads over the right ventricle, but became inverted in Leads V_5 and V_6 and showed slight inversion of the terminal phase in Lead aV_F . On the basis of the changes in Leads aV_F and aV_L , a diagnosis was made of recent posterolateral infarction. The depression of the RS-T segment in Leads V_1 through V_4 was considered reciprocal to the elevation in Lead aV_F . On the other hand, the depression of the RS-T segment in Lead aV_L was attributed to extension of the infarct subendocardially into the lateral wall because of the concurrent development of an abnormal Q wave in this lead.

Pathologic Findings.—The heart weighed 443 grams and exhibited a large recent infarct, which involved the entire posterolateral wall of the left ventricle and extended into the septum at the base, as outlined in the roentgenogram reproduced in Fig. 4. By microscopic examination, the infarct was judged to be less than twenty-four hours in age and was found to be transmural in distribution in the lateral as well as in the posterior wall. In view of the pathologic findings,

an abnormal QS or QR complex would have been expected in Lead aV_F . A broadened and notched R wave may have been registered in this lead because of insufficient duration of the degenerative changes in the posterior wall for obliteration of the response to the activating impulse. The

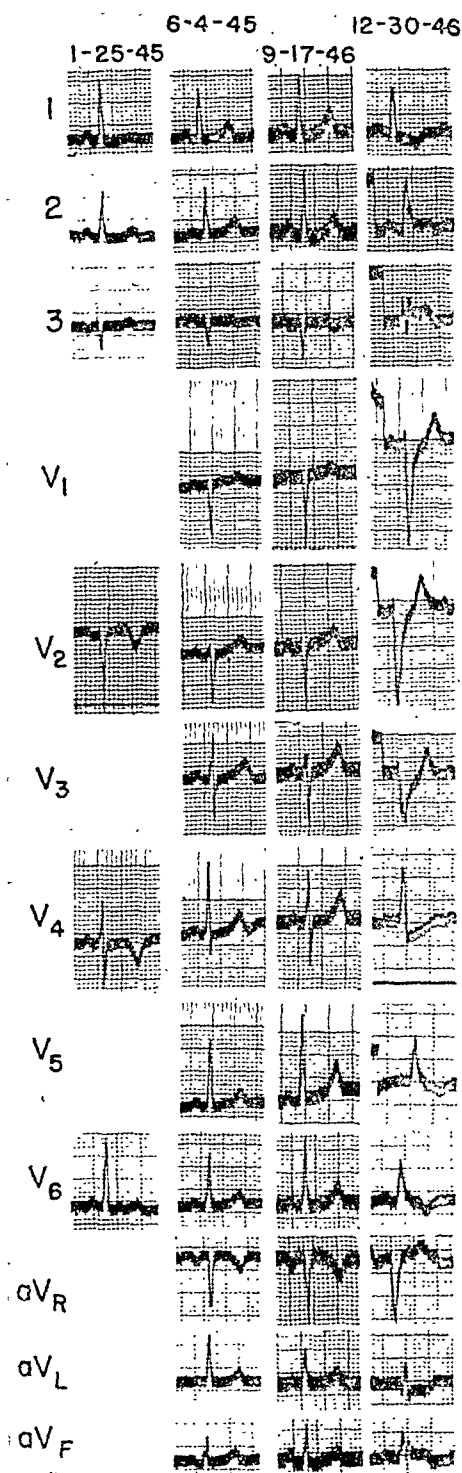


Fig. 3.—Serial electrocardiograms in Case 125, showing recovery from an anteroseptal infarction and a terminal posterolateral infarction.

abnormal QR pattern and depression of the RS-T segment in Lead aVL might have reflected a more advanced lesion in the subendocardial than in the subepicardial portion of the lateral wall at the time the electrocardiogram was taken. Although the infarct reached the junction of the anterior and lateral walls in the two basilar segments, it is probable that the depression of the RS-T segment in Leads V₁ through V₄ was a reciprocal manifestation of the acute posterolateral infarct. Multiple small areas of fibrosis were found in the subendocardial half of the antero-septal wall of the left ventricle about midway between apex and base, as indicated by the stippling in Fig. 4, and were considered to be a residue of a healed, patchy, subendocardial infarct. An acute patchy infarct in this area in January, 1945, could have accounted for the T-wave changes in the first tracing, and a subsequent return of a considerable portion of the myocardium to normal could account for the disappearance of all traces of this antero-septal infarct from the electrocardiogram.



Fig. 4.—Roentgenogram of the injected heart in Case 125 with a large posterolateral infarct demarcated by solid lines and a healed, patchy antero-septal infarct demarcated by stippling.

CASE 126.—A 55-year-old chronic alcoholic man was in good health until Feb. 16, 1943, when he had an attack of prolonged retrosternal constriction, complicated by congestive failure, and leading to admission two weeks later. The hospital course was uneventful and there were no further cardiovascular symptoms during the remaining year of his life. He returned on Jan. 31, 1944, with a typical history of carcinoma of the stomach, beginning in the fall of 1943. The lesion proved inoperable and resulted in death on April 18, 1944.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 5 were selected from a series obtained during his two hospital admissions. Four cat units of digitalis were given prior to the tracing of March 2, 1943, but the drug was subsequently discontinued. The abnormal QRS-T pattern in Leads II and III of the first electrocardiogram was typical of a recent posterior myocardial infarct. Lead V₆ on this occasion showed a normal R wave, an isoelectric RS-T

junction, and an upright T wave. The subsequent development of a distinct Q wave in Lead V_6 , accompanied by reduction in the R wave, transient elevation in the RS-T junction, and inversion of the T wave, indicated extension of the posterior infarct into the lateral wall of the left ventricle. The signs of the lateral infarction did not become evident in the standard leads. The T waves in Leads II and III meanwhile showed deepening inversion typical of an organizing posterior infarct. There was a concurrent reciprocal increase in the height of the upright T waves of Leads V_2 and V_4 . On Feb. 1, 1944, there was a shifting supraventricular pacemaker. Comparison of this tracing with those taken the previous year showed no significant change in the abnormal QR complex of Leads II and III. The T waves in Leads II and III were still sharply inverted and comparable in contour to those of the preceding year, but smaller in voltage. Thus, the pattern of organizing posterior infarction had become fixed. Positive findings of posterior infarction were evident in Lead aV_F . On the other hand, the electrocardiographic signs of the lateral extension had disappeared from Lead V_6 . The cycle of V_6 from the tracing of February 1,

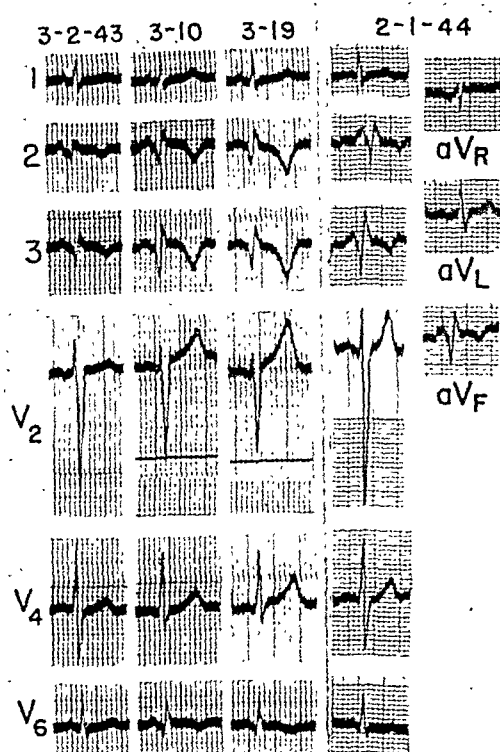


Fig. 5.—Serial electrocardiograms in Case 126.

reproduced in Fig. 5, showed downward drifting of the string between the P wave and the QRS complex, which at first glance might be taken for a Q wave; however, inspection of other cycles in the same lead showed that the Q wave was absent and that the findings in the reproduced cycle represented an artifact from an unstable isoelectric line. The T wave in Lead V_6 had become upright and the entire pattern in this lead, as well as that in Lead I, corresponded closely with that registered in the respective leads of the initial tracing of March 2, 1943.

Pathologic Findings.—The heart weighed 225 grams and revealed an old, completely healed posterolateral infarct, extending from the atrioventricular groove to a point 1.0 cm. above the apex. The infarct was similar in size and distribution to the posterior portion of the infarct which occupied the second, third, fourth, and fifth segments of the heart in Case 125 (Fig. 4). The posterior wall in this area was completely replaced by fibrous tissue and was reduced to a thickness of 2.5 mm., as compared with an average thickness of 13 mm. of the remaining uninfarcted portion

of the left ventricle. Thus, there was good correspondence between the fixed pattern in Lead aV_F and the complete fibrous replacement of the posterior wall. Since this pattern corresponded closely with the reciprocal of that in Lead V_4 , it probably represented transmission of cavity potentials through the posterior wall and diaphragm to the left leg. The extension of the infarct into the lateral wall was sufficient to account for the acute changes in Lead V_6 on the first admission. The disappearance of these findings with healing of the infarct was probably due to the fact that the apical portion of the lateral wall was not infarcted and probably exerted the preponderant effects on the potential variations of the electrode at Position V_6 .

CASE 127.—A 68-year-old man gave a history of myocardial infarction in 1941, with complete recovery. He had a transient attack of retrosternal oppression on Sept. 8, 1943, and two days

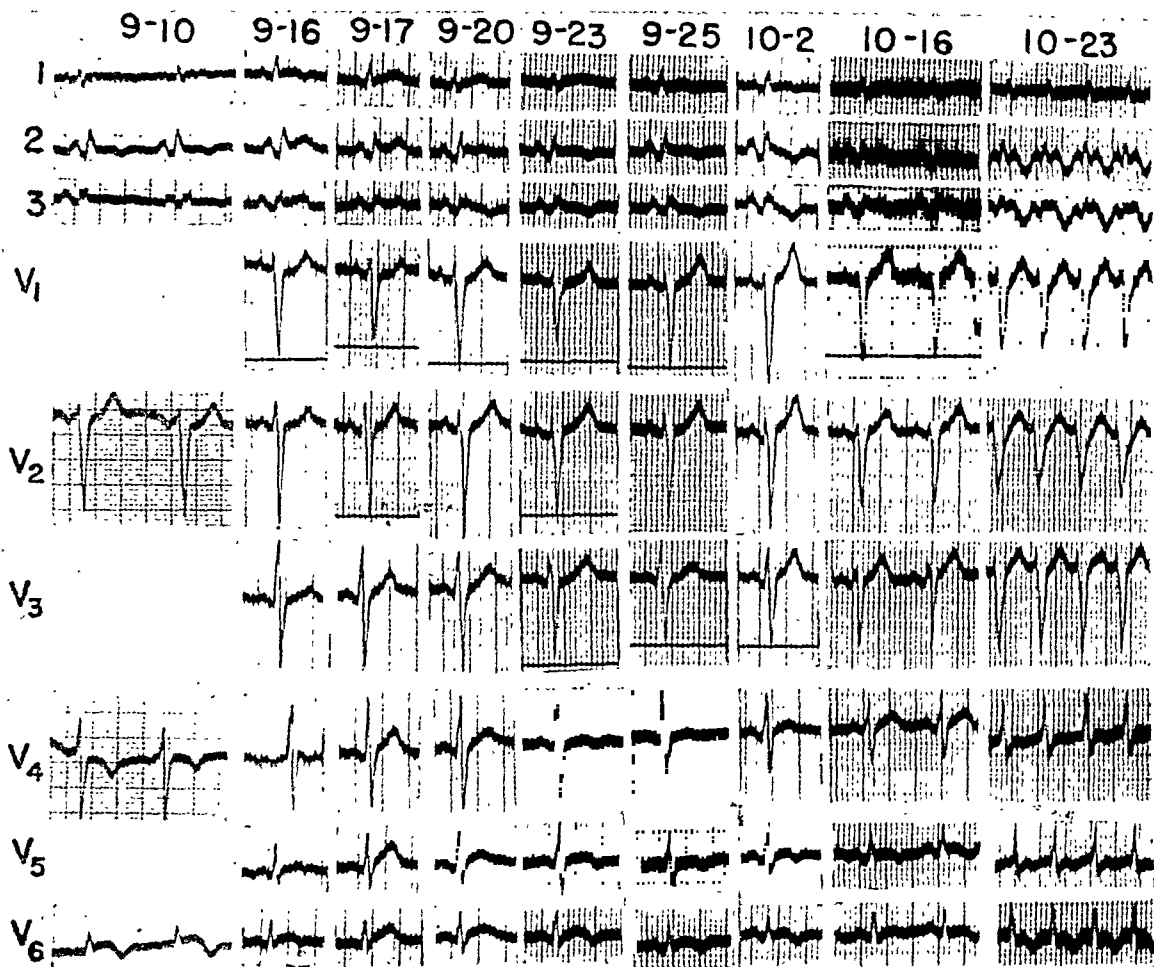


Fig. 6.—Serial electrocardiograms in Case 127.

later was awakened by a more severe episode. After resuming work on September 14, he was seized by a much more severe attack and was brought to the hospital in shock with right hemiparesis. Blood pressure was unobtainable for twenty-four hours. A saddle embolus at the bifurcation of the aorta occurred on September 25, but color gradually returned after Dicumarol therapy. He suddenly collapsed on October 22 with the advent of auricular flutter and died the following day. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 6 include a tracing taken by his family physician on September 10, five hours after the attack of pain which awakened him from sleep. Leads II, III, and V_6 of this tracing showed a small, slurred or notched R wave, an abnormally elevated RS-T junction, and inversion of the terminal portion of the T wave, in-

indicative of a recent patchy infarct of the posterolateral wall of the left ventricle. The inversion of the T wave in Lead V_4 may have been the result of an outlying zone of ischemia, and the apparent depression of the RS-T segment in Lead V_2 was largely an artifact consequent upon an unstable isoelectric line. Although there was no significant change in the QRS complex on September 16, the increased elevation of the RS-T junction and the change to a monophasic upright T wave in Leads II and III suggested further injury to the posterior wall of the left ventricle. Lead aV_F was not obtained until later in the hospital course and at that time showed an abnormal QR pattern of low voltage similar to that of Lead III. The marked elevation of the RS-T junction in Leads V_4 through V_6 , which appeared on September 17, might have been due to extension of the lateral portion of the infarct further into the anterior wall or to complicating pericarditis. Because of the absence of significant change in the QRS pattern in these leads in subsequent tracings and the rapid evolution of the T waves in a fashion typical of pericarditis, the RS-T changes in Leads V_4 and V_6 were attributed to extension of the pericarditis into the anterolateral wall. The final tracing on October 23 showed auricular flutter with a 2:1 ratio. There was no evidence to suggest further extension of the posterolateral ventricular infarct.

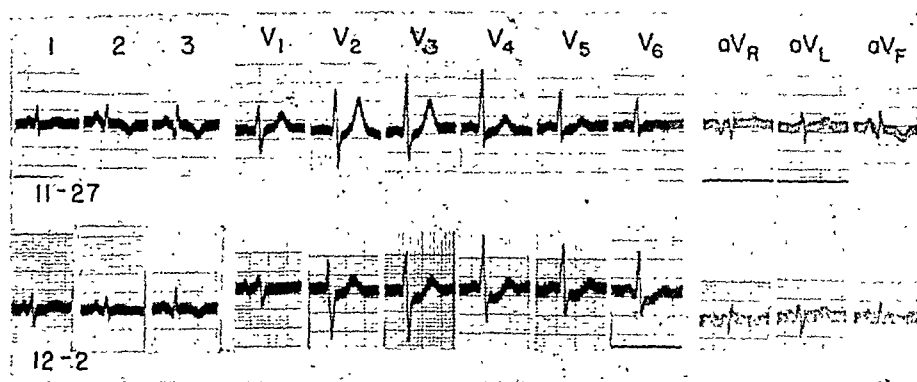


Fig. 7.—Serial electrocardiograms in Case 128.

Pathologic Findings.—The heart weighed 500 grams and exhibited a large, organizing posterolateral infarct, similar in size and position to the lesion in the first five segments in Case 125 (Fig. 4). This infarct was presumably responsible for the abnormalities in Leads aV_F , II, III, and V_6 . There was a small, completely healed infarct confined to the anterosseptal aspect of the apical third of the left ventricle. The absence of electrocardiographic signs of this infarct was probably explained by a patchy character and lack of any recent activity. There was a marked fibrinous pericarditis, which was extended onto the anterior aspect of the left ventricle. This was probably responsible for the serial changes in the RS-T segment and T wave beginning on September 17. There was a saddle embolus at the bifurcation of the aorta and a large, residual mural thrombus at the site of the posterolateral infarct.

CASE 128.—A previously healthy 54-year-old man was suddenly seized with retrosternal oppression and dyspnea at 1:00 A. M. on November 26 and was brought to the hospital one hour later. His symptoms were relieved by morphine and his course was uneventful until 7:00 P. M. on December 4, when there was a recurrence of severe retrosternal constriction complicated by shock and followed by death fifteen hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms obtained on November 27 and December 2 are reproduced in Fig. 7. An earlier tracing, taken nine hours after the onset of the present illness, showed a wandering pacemaker with episodes of interference dissociation. The QRS pattern in Lead aV_F was similar to that on November 27, which was characterized by a slurred Q wave that was 0.03 second in duration and approximately 50 per cent of the amplitude of the succeeding R wave. This pattern, together with the sharp inversion of the T wave, was typical of an organizing posterior infarct. The R and T waves in the first four precordial leads were unusually tall and the RS-T segments in Leads V_2 through V_4 were abnormally depressed. These

findings constituted classical reciprocal effects of posterolateral infarction. However, Leads V_3 and V_6 in this case showed no definite evidence of involvement of the lateral wall. Lead aV_L apparently reflected the potential variations of the right side of the precordium, rather than the lateral wall of the left ventricle, as judged by its resemblance to Lead V_1 . On December 2 an abnormal QR pattern was still present in Lead aV_F . The RS-T junction in this lead remained isoelectric and the T wave was less deeply inverted. A striking change had occurred in the precordial leads and was characterized by the development of marked depression of the RS-T segment in Leads V_6 and V_5 and a significant increase in the downward displacement of the RS-T junction in Leads V_2 through V_4 , together with decrease in the voltage of the upright T waves in these leads. Three possibilities were given serious consideration: an acute ischemia of the subendocardial portion of the anterolateral wall, a patchy infarction in this region, and an increased reciprocal effect secondary to further acute injury of the subendocardial portion of the posterolateral wall. The last named seemed less likely because of absence of elevation of the RS-T segment in Lead aV_F . A positive decision could not be reached between the two former possibilities.

Pathologic Findings.—The heart weighed 440 grams and exhibited a recent posterolateral infarct which occupied a position almost identical with that in Case 125 (Fig. 4), except that it was limited to the subendocardial half of the wall. In the second, third, and fourth segments it extended into the subendocardial half of the lateral wall, reaching a point in the lateral wall comparable to that reached in the fifth segment of Fig. 4. The involvement of the subendocardial half of the posterior wall accounted for the abnormal QR pattern in Lead aV_F . The extension into the subendocardial half of the lateral wall may have accounted for the acute depression of the RS-T segment in Leads V_5 and V_6 . The findings in Leads V_1 through V_4 were presumably reciprocal, since the infarct did not extend far enough anteriorly to affect directly the pattern in these leads. It is possible, however, that a pathologically unrecognized ischemia of the subendocardial portion of the anterior wall might have accounted for the acute depression of the RS-T segment in the last tracing.

CASE 129.—A 60-year-old man was first admitted to the hospital in August, 1944, because of lobar pneumonia. He had had hypertension and exertional dyspnea for eight years and dependent edema for three years, but gave no definite history of myocardial infarction. He continued to have exertional dyspnea after discharge, but had no chest pain. He remained ambulatory until 7:00 P. M. on March 5, 1945, when he was suddenly seized with severe abdominal pain and vomiting, and was admitted the following morning in collapse. A clinical diagnosis of mesenteric thrombosis was made. Death occurred on March 7.

Electrocardiographic Findings.—Electriccardiograms reproduced in Fig. 8 were obtained on Aug. 15, 1944, after the patient's recovery from pneumonia and while he was on maintenance doses of digitalis, and on March 7, 1945, six hours before death, while he was taking no cardiac glycosides. Auricular fibrillation was consistently present. An abnormal QR complex was found in Leads aV_F and aV_L and was indicative of posterolateral infarction. The involvement of the subendocardial portion of the lateral wall was supported by the findings in Leads V_5 and V_6 . Although the Q wave in these leads was only 4.0 mm. in depth and about 20 per cent of the amplitude of the succeeding R wave, it was considered abnormal because the time interval from its onset to its nadir was 0.03 second and because of the slurring and prolongation of the ascending limb of the R wave. Esophageal leads were obtained in order to investigate further the lesion of the posterior wall. Leads at the ventricular level showed an initial Q wave, 3.0 to 5.0 mm. in depth, 0.03 to 0.04 second in duration, and 25 to 50 per cent of the amplitude of the succeeding R wave. These findings, together with the slurring of the ascending limb of the R wave, were regarded as confirmatory evidence of infarction of the subendocardial portion of the posterior wall. The abnormal Q waves in Leads I and II were due as much to the initial positivity of the right arm as to the initial negativity of the left arm and leg. Although a QR complex indicative of posterior infarction was recorded in Lead aV_F , an RS deflection, in no way suggestive of posterior infarction, was registered in Lead III. Since the RS complex in Lead III was the approximate reciprocal of the QR pattern in Lead aV_L , it would appear that the potential variations of the left arm component of Lead III preponderated over those of the left leg component in this case. From the contour of the T waves, it was believed that the posterolateral infarct was old and

healed. The R wave did not show the expected increase in amplitude as the electrode was moved from precordial Positions 1 to 3 and actually was very slightly smaller in Lead V_2 than in Lead V_1 . Although this finding was in keeping with an old, completely healed anteroseptal infarction, it was not sufficiently striking to justify the diagnosis. The inverted T waves in Leads V_2 and V_3 on August 15, 1944, were not typical of infarction, but were not satisfactorily accounted for. In the tracing of March 7, 1945, there was no significant change in the QRS pattern in the limb leads or in Leads V_5 and V_6 . Signs of the old, healed posterolateral infarction were still evident in Leads aV_R , aV_L , V_5 and V_6 . The only significant change occurred in the first four precordial leads. The initial phase of the QRS complex was upright in the first three precordial leads and averaged 4.0 mm. in Leads V_1 and V_2 but fell off to 2.0 mm. in Lead V_3 . In Lead V_4 there was a 1.0 mm. Q wave followed by an R wave, which averaged 7.0 millimeters. The RS-T junction was elevated approximately 1.0 mm. in Leads V_1 through V_3 and was isoelectric in Lead V_4 . The T wave was sharply inverted in these leads and reached its greatest depth in Lead V_3 . The question arose as to whether these changes were representative of a recent anteroseptal infarct, an old anteroseptal infarct with recent reinfarction or ischemia, or acute right ventricular dilata-

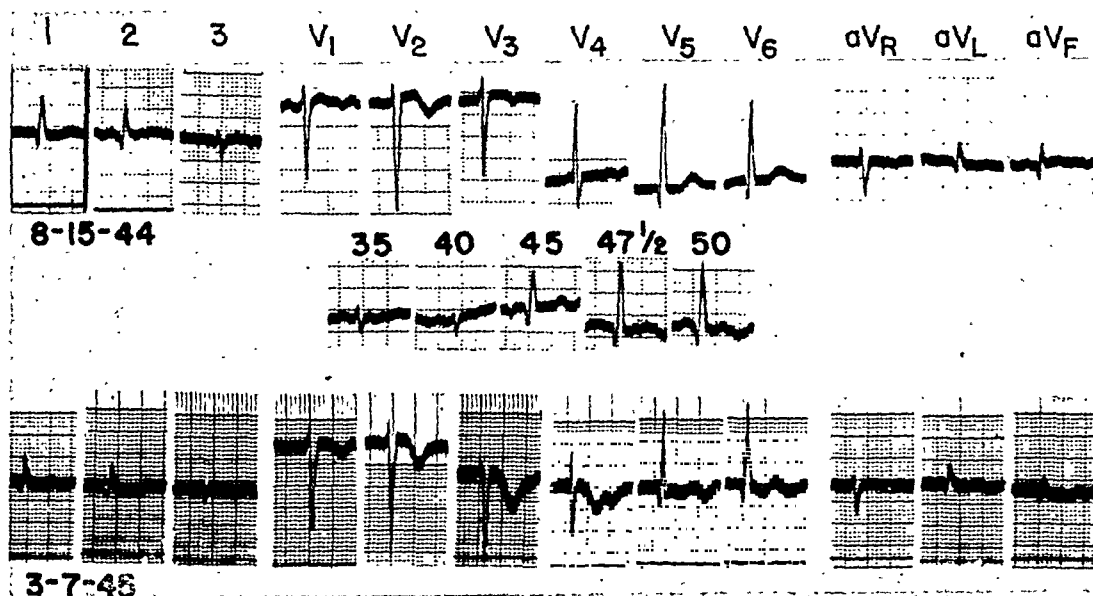


Fig. 8.—Serial electrocardiograms in Case 129, showing old, healed posterolateral infarction and terminal anteroseptal infarction. The tracings in the middle row are esophageal leads at indicated levels.

tion. The last named was considered less likely because the maximal T-wave inversion was found in Leads V_3 and V_4 rather than in V_1 and V_2 and, more important, because it failed to account for the abnormalities in the initial phase of the QRS complex in Leads V_3 and V_4 . These changes pointed toward a recent, patchy subendocardial infarct in the anteroseptal portion of the left ventricle.

Pathologic Findings.—Death was due to thrombosis of the superior mesenteric artery. The heart weighed 676 grams and revealed multiple old infarcts, situated as outlined in Fig. 9. In the apical segment there was a semilunar infarct involving the subendocardial half of the anterolateral and posterior walls. Higher in the ventricle the infarct was divisible into three separate portions. The largest occupied the subendocardial one-half to two-thirds of the posterior wall and extended from apex to base. A second infarct involved the subendocardial one-half to two-thirds of the lateral wall in the fourth and fifth segments and became more anterior at the base. Microscopic examination of these two infarcts at various levels showed patchy to dense fibrosis without evidence of recent activity. A third infarct was located in the subendocardial one-third

to one-half of the anteroseptal area, as demarcated by broken lines in Fig. 9. Microscopic examination of this lesion showed patchy fibrosis, which was a residue of a remote infarction with recent cellular infiltration, which was attributed to terminal reinfarction. Thus, the pattern in Lead aV_F and the esophageal leads could be correlated with the old, subendocardial posterior infarction, whereas that in Leads aV_L , V_5 , and V_6 corresponded with the old, subendocardial lateral infarction. The acute changes in the first four precordial leads on March 7, 1945, were apparently the result of acute infarction in an area of old, healed anteroseptal fibrosis. This was regarded as secondary to the vascular collapse produced by the mesenteric thrombosis.

CASE 130.—A 45-year-old woman was perfectly well until 11:00 P. M. on Oct. 31, 1944, when she was suddenly taken with sharp retrosternal pain, lasting about one-half hour, accompanied by cough and followed by gross hemoptysis. There was no clinical evidence of phlebothrombosis or pulmonary embolism. Physical examination revealed hyperthyroidism, later confirmed by

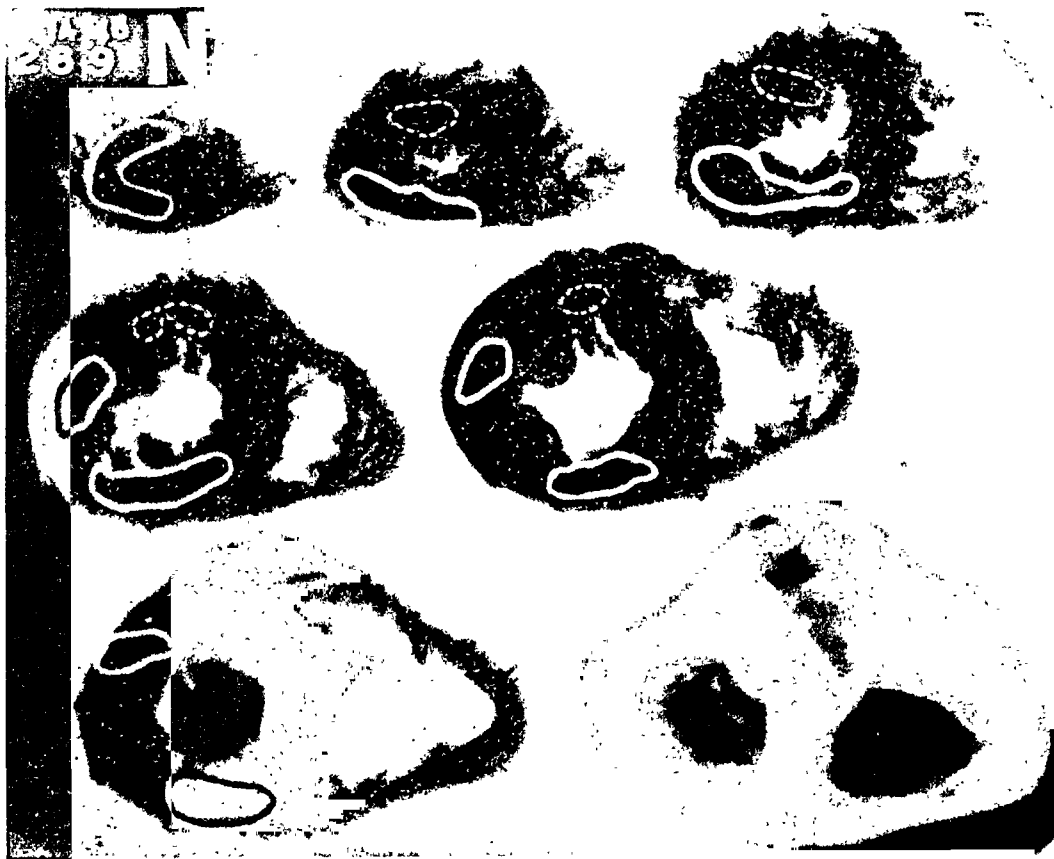


Fig. 9.—Roentgenogram of the injected heart in Case 129, showing old, healed posterolateral infarction in solid outline and recent patchy anteroseptal infarction in broken outline.

the basal metabolic rate. After a month in the hospital, the patient failed to report for observation for a year, when she returned in thyroid crisis and died on Nov. 25, 1945. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram reproduced in Fig. 10, *A* was taken thirty-six hours after the onset of the attack of retrosternal pain. The Q wave recorded in Lead aV_F was 0.02 second in duration, 2.5 mm. in depth, and one-third of the amplitude of the succeeding R wave. From this borderline Q wave, together with the associated elevation of the RS-T segment, a diagnosis of recent posterior infarction was made. A borderline QR complex with a ratio of 20 per cent was found in Leads V_4 and V_6 . Because of the abnormal elevation of the RS-T segment in these leads, the findings were attributed to extension of the infarct subendocardially into the lateral wall of the left ventricle. Lead aV_L showed an RS pattern like that of Lead V_4 and thus gave no help in the delineation of the lateral infarction. However, the diag-

nosis of posterolateral infarction was confirmed by the classical evolution of the RST-T pattern in Leads aV_F , V_6 , and V_6 of serial tracings over the next month. Leads II and III also revealed signs of posterior infarction. The distinct Q wave in Lead I was not due to initial negativity of the left arm, since no Q wave was demonstrable in Lead aV_L . It was a manifestation of initial positivity of the right arm, as shown by its correspondence with the reciprocal of the pattern in Lead aV_R .

Pathologic Findings.—The heart weighed 449 grams and revealed an old, healed posterolateral infarct with an overlying organized pericarditis. The distribution of the lesion in the first, second, fourth, and fifth segments was almost identical with that in the corresponding segments in Case

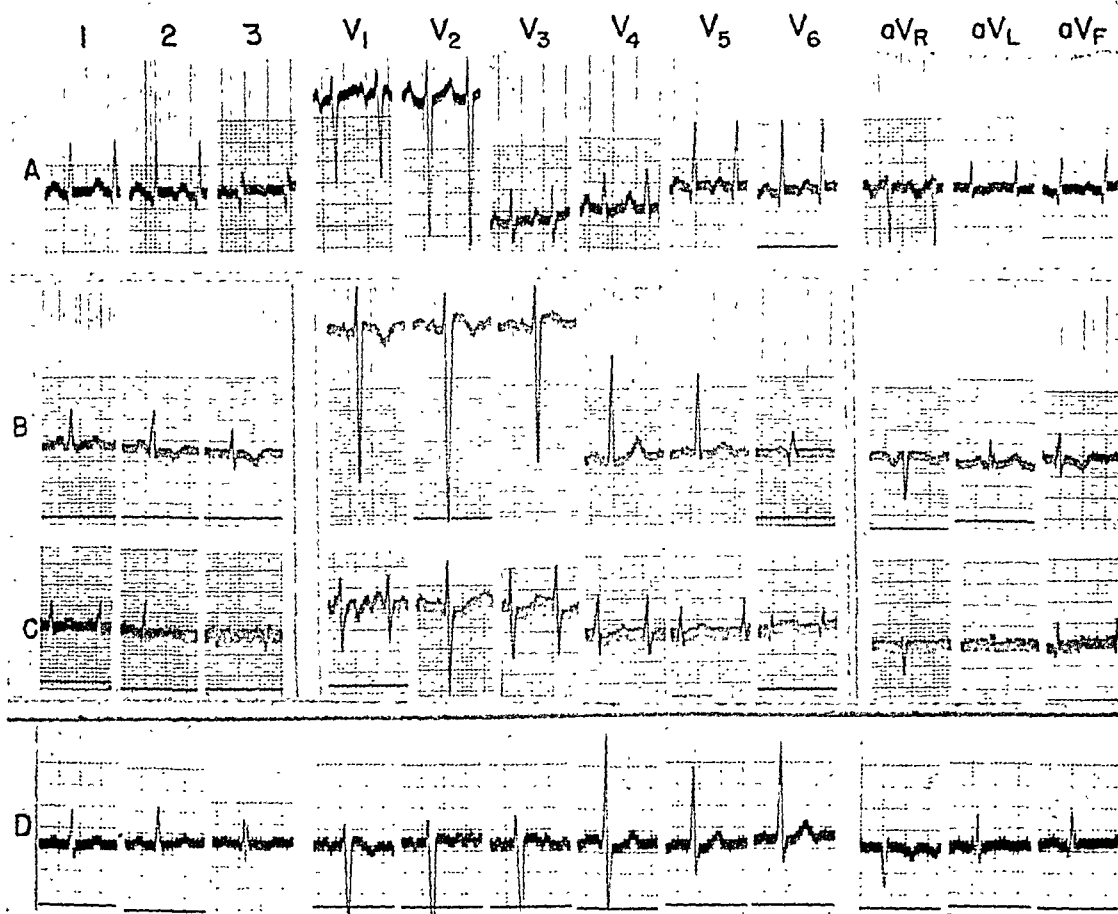


Fig. 10.—Electrocardiographic findings in posterolateral infarction. A, Case 130; B, Case 131; C, Case 132; and D, Case 133.

132 (Fig. 11). In the third segment in this case, the infarct did not extend as far into the lateral wall as in this segment in Case 132. Thus, there was good correlation between the electrocardiographic findings and those at necropsy.

CASE 131.—A 59-year-old woman gave a history of a sudden onset of severe retrosternal constriction and dyspnea four months previously, leading to hospitalization elsewhere. With resumption of ambulation, angina pectoris occurred. During the fortnight immediately preceding entry, she had repeated paroxysms of nocturnal dyspnea. There was marked pulmonary congestion and edema on admission, but no evidence of right heart failure. Compensation was gradually restored, but congestive failure recurred after discharge, ending in death three months later.

Electrocardiographic Findings.—An electrocardiogram reproduced in Fig. 10, *B* was obtained on the fifth hospital day, after the administration of a total of 1.4 Gm. of digitalis. In Lead aV_F there was an initial Q wave 1.0 mm. deep and approximately 15 per cent of the succeeding R wave. Although the QR ratio was within normal limits, the association of a definite Q wave with notching and prolongation of the ascending limb of the R wave indicated that the QR complex was abnormal. These findings were interpreted as evidence of patchy infarction of the posterior wall of the left ventricle. The isoelectric RS-T junction and inverted T wave in Lead aV_F were most likely a residue of an old infarct, but were compatible with the stage of organization. The findings in Lead aV_F carried over into Leads II and III. In Lead aV_L there was a Q wave of 0.5 mm., fol-

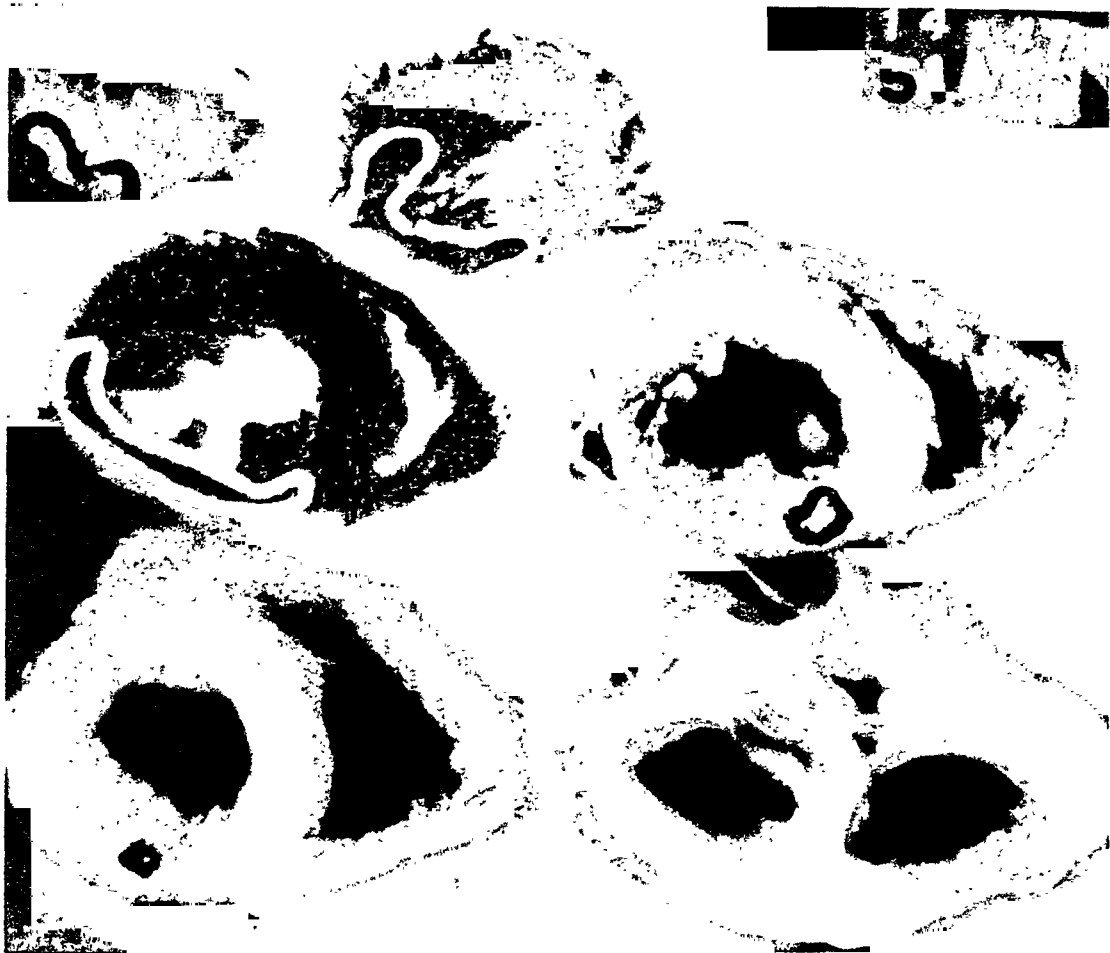


Fig. 11.—Roentgenogram of the injected heart in Case 132, showing the position of the posterolateral infarct.

lowed by a precipitous upstroke and then a coarse, broad notch on the downstroke of the R wave. The QRS pattern in this lead was thus abnormal, but was not specific for infarction. On the other hand, the presence of a Q wave in Lead V_6 after an upright initial deflection in the other five precordial leads, together with a marked reduction in the amplitude of the R wave in Lead V_6 in comparison with that of Lead V_5 , was indicative of extension of the posterior infarct into the lateral wall of the left ventricle. The Q wave in Lead V_6 was 2.0 mm. deep and approximately 50 per cent of the succeeding R wave. The RS ratio in the first three precordial leads indicated that the electrode was to the right of the interventricular septum. The R wave of Lead V_2 was slightly smaller than that of Leads V_1 and V_3 , but the reduction was not sufficiently great

to be of diagnostic significance. Although inversion of the T wave in Leads V_1 and V_2 may occur as a normal variant, the elevation of the RS-T junction in these leads suggested that the RS-T segment and T complexes were abnormal. The T-wave changes in Leads V_1 and V_2 were considered independent of digitalis because of the contour of the RS-T segment and because the Q-T interval was at the upper limit of normal. The diagnosis rested between acute anteroseptal ischemia, a recent intramural anteroseptal infarction, and acute right ventricular dilatation. The last alternative was favored because of the maximal T-wave changes in Lead V_1 and was compatible with the marked pulmonary congestion and edema still present at the time the electrocardiogram was taken.

Pathologic Findings.—Necropsy revealed considerable left ventricular hypertrophy and disclosed an old, completely healed infarct of the posterolateral aspect of the apical portion of the left ventricle, comparable in size and position with that in Case 132 (Fig. 11). From its position, the infarct adequately accounted for the abnormal patterns in Leads aV_F and V_6 . Since the anterior walls of the left ventricle and septum were not infarcted, the findings in Leads V_1 and V_2 were due either to acute right ventricular dilatation or anteroseptal ischemia, more likely the former.

CASE 132.—A 64-year-old woman was admitted to the hospital because of gangrene of the left leg. She gave a typical history of angina pectoris of two years' duration. No definite history of myocardial infarction or of cardiac failure could be elicited. The patient died of a cerebral vascular accident on the twentieth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the third hospital day, after the administration of 1.1 Gm. of digitalis, is reproduced in Fig. 10, C. Auricular fibrillation was present with a rapid ventricular rate. The initial phase of the QRS complex was upright in the first five precordial leads and the R wave was relatively tall in Leads V_1 through V_3 . The marked reduction in the R wave and the appearance of a relatively large Q wave as the electrode was moved from Position 5 to Position 6 was indicative of infarction of the lateral wall of the left ventricle. The elevation of the RS-T junction and the monophasic upright T wave suggested a recent lesion. The depression of the RS-T segment in Leads V_2 through V_4 might have been reciprocal to the elevation in Lead V_6 or could have been a manifestation of digitalis action. No evidence of the lateral infarction was registered in Lead aV_L or in the standard leads. The small, notched QRS complex in Lead aV_L suggested that the potential variations of the anterior aspect of the left ventricle near the transitional zone were being referred to the left arm. In Lead aV_F , however, there was a QR complex, the Q wave ranging from one-fourth to one-third of the amplitude of the R wave. This was a borderline finding, which was suggestive, but not diagnostic, of extension of the lateral infarct into the posterior wall of the left ventricle. Thus, the electrocardiogram was diagnostic of lateral infarction and suggestive of coexistent posterior infarction.

Pathologic Findings.—The heart weighed 362 grams and revealed an old, completely healed infarct of the apical three-fifths of the posterolateral aspect of the left ventricle, as outlined in Fig. 11. The infarct was limited to the subendocardial one-half to three-fourths of the posterior wall, but was transmural in a portion of the lateral wall. There was good correspondence between the abnormal QR pattern in Lead V_6 and the lesion of the lateral wall. There was an overlying chronic epicarditis, which might have been a factor in the elevation of the RS-T segment and the monophasic upright T wave. It is also possible that this was a fixed pattern associated with an old, completely healed lateral infarct. The borderline QR complex in Lead aV_F was apparently a manifestation of the posterior portion of the infarct.

CASE 133.—A 38-year-old man was hospitalized because of mental confusion and convulsions due to hypertensive encephalopathy. He had had hypertension for ten years and had been treated in another hospital five years previously for coronary thrombosis. There was no history of subsequent infarction or angina pectoris. Maintenance doses of digitalis had been instituted before admission and were continued during hospitalization. Death from bronchopneumonia occurred on the twenty-eighth day.

Electrocardiographic Findings.—An electrocardiogram obtained upon the first hospital day is reproduced in Fig. 10, D. The prominent R wave in Leads V_4 through V_6 , together with the 0.05 second interval from onset to peak of this deflection, suggested left ventricular hypertrophy. The T-wave pattern, however, was not characteristic. The Q wave recorded in Lead aV_F was 0.02 second in duration, 1.5 mm. in depth, and 25 per cent of the succeeding R wave. The ascending limb of the R wave was fairly steep, consuming 0.03 second from onset to peak, but the descending limb was coarsely notched. The QR pattern in Lead aV_F was borderline and was somewhat suggestive of a subendocardial posterior infarction. In Lead aV_L there was coarse notching of the ascending limb of the R wave. This, together with a time interval of 0.07 second from onset of the QRS complex to the peak of the R wave, was distinctly abnormal and compatible with, though not diagnostic of, a conduction defect in the lateral wall of the left ventricle. These findings, taken in conjunction with those in Lead aV_F , were suggestive of an old, subendocardial posterior infarction, extending in patchy fashion through the lateral wall of the left ventricle.



Fig. 12.—Roentgenogram of the injected heart in Case 133, showing the position of the posterolateral infarct.

Pathologic Findings.—The heart weighed 788 grams and exhibited an old, completely healed posterolateral infarct, as outlined in Fig. 12. Portions of the infarct were transmural and other portions were limited to the subendocardial two-thirds. Microscopic examination revealed islands of intact muscle interspersed through the infarct. This, together with the lack of high axillary leads, may have accounted for the paucity of electrocardiographic findings. Defective conduction through the lateral and posterior walls of the left ventricle secondary to the infarct could explain the pattern in Leads aV_L and aV_F . A fibrinous pericarditis secondary to uremia was found at autopsy. This may have accounted for the presence of upright, rather than the usual inverted, T waves in Leads V_4 through V_6 associated with the QRS pattern of left ventricular hypertrophy.

CASE 134.—A 56-year-old man, who had had hypertension for at least four years, was suddenly seized with extreme dyspnea while driving his car. Chest pain was denied. He was brought directly to the hospital and arrived moribund in left ventricular failure. Death occurred on the third hospital day.

Electrocardiographic Findings.—The electrocardiogram is not reproduced because of its close resemblance to that in Case 133 (Fig. 10, D). The QRS pattern in the precordial leads was typical of left ventricular hypertrophy. Abnormal depression of the RS-T segment was found in the precordial leads over the left ventricle and was attributed in part to left ventricular hypertrophy and in part to superimposed effects of 0.8 mg. of Cedilanid, administered before the electrocardiogram was obtained. In Lead aV_L there was coarse slurring at the base of the ascending limb of the R wave in place of the notching in the corresponding lead of Fig. 10, D. The delayed attainment of the peak of the R wave, depressed RS-T junction, and inverted T wave of this lead were ascribed to left ventricular hypertrophy. In Lead aV_F, there was an initial Q wave followed by a coarsely notched M-shaped R wave. The Q/R ratio was 33 per cent. These changes were attributed to defective conduction in the posterior wall, secondary to subendocardial infarction. Because of the type of QRS pattern and the lack of typical changes in the RS-T segment and T wave, it was postulated that the infarct was old and healed.

Pathologic Findings.—The heart weighed 1,104 grams as a result of extreme left ventricular hypertrophy. Old healed infarcts were found in the posterior and lateral aspects of the left ventricle, which corresponded closely in distribution to the lesions in Case 129 (Fig. 9), demarcated by solid lines. At the apex there was a single infarct occupying the subendocardial half of the posterolateral wall. Toward the base, this infarct split into two separate lesions, a patchy posterior infarct, similar in position to that of Fig. 9, and a somewhat denser infarct of the subendocardial half of the lateral wall. This infarct, like that in Case 129, shifted into a more anterolateral position at the base. The type of lesion in the posterior wall found at autopsy corresponded closely with the electrocardiographic findings in Lead aV_F. The lateral infarct had been missed electrocardiographically, probably because it occupied a relatively small portion of the markedly hypertrophied lateral wall.

CASE 135.—A 42-year-old man had had transient attacks of retrosternal oppression, provoked by exercise and relieved promptly by rest, for fifteen years and was admitted to the hospital following three weeks of almost continuous angina decubitus. There were physical signs of rheumatic aortic stenosis and insufficiency complicated by hypertension. The patient continued to have prolonged attacks of chest pain during his hospital stay and died on the tenth day.

Electrocardiographic Findings.—An electrocardiogram obtained four hours after admission and before the administration of digitalis was reproduced in a previous communication,⁷ Fig. 7, Case 16. In Lead V₆ there was a prominent slurred R wave, a slightly delayed intrinsicoid deflection, a depressed RS-T junction, and an inverted T wave, which were considered typical of left ventricular hypertrophy. The diagnosis was supported by the exceptionally deep, slurred S wave in Leads V₁ through V₃. Lead aV_L displayed a minute Q wave 0.5 mm. in depth and 0.02 second in duration, followed by a slurred ascending limb of the R wave, 11 mm. in height and 0.06 second in duration. The RS-T junction was isoelectric and the T wave was inverted. The QRS pattern in Lead aV_L was indicative of defective conduction in the lateral wall of the left ventricle and might have been the result of left ventricular hypertrophy with patchy fibrosis or a patchy infarction of the lateral wall of the left ventricle. Lead aV_F exhibited a QS complex with marked slurring and notching of its terminal limb. The question arose as to whether the findings in Lead aV_F were the result of a posterior infarct or were merely due to horizontal position with transmission of potential variations of the posterior inferior surface of the right ventricle to the left leg. The former alternative was preferred in the ante-mortem interpretation because of the late R equivalent and a diagnosis was made of posterolateral infarction, probably old.

Pathologic Findings.—The heart weighed 602 grams as a result of left ventricular hypertrophy secondary to rheumatic aortic stenosis and exhibited an organizing posterolateral infarct of one to two months' duration. The infarct involved the second and third segments in a fashion comparable to that in the corresponding segments in Case 133 (Fig. 12). The involvement of the

fourth segment was closely comparable, both in size and position, to the lesion in the fifth segment of Fig. 12. On microscopic examination, the infarct appeared dense in the subendocardial one-fourth and patchy in the remainder of the wall. The findings in Lead aV_L could be correlated satisfactorily with the lateral portion of the infarct. On restudy of the case, however, it is doubtful that the posterior part of the infarct was responsible for the findings in Lead aV_F , since too small a fraction of the posterior wall was involved to account for a QS complex. It is more likely that the heart was in horizontal position and that the QS complex recorded in Lead aV_F was transmitted from the epicardial surface of the posteroinferior aspect of the right ventricle to the left leg.

CASE 136.—A 52-year-old man was first admitted to the hospital three days after the onset of a prolonged attack of oppressive retrosternal pain. Convalescence was uneventful and the patient had no further attacks of thoracic pain. Seventeen months later he was readmitted with typical signs of a saddle embolus at the bifurcation of the aorta complicated by acute left ventricular failure. Death occurred nine hours after the onset of symptoms referable to the saddle embolus.

Electrocardiographic Findings.—Electrocardiograms taken during the first admission included only the three standard limb leads and precordial Leads V_2 , V_4 , and V_6 . Five tracings taken over a period of two weeks showed a constant QRS-T pattern in the standard leads. This consisted of a prominent R_1 and an upright T_1 ; a triphasic QRS complex in Lead II, consisting of a 1.0 mm. Q wave, a 6.0 mm. R wave, and a 1.0 mm. S wave, with an isoelectric RS-T segment and an upright T wave; and a notched QS complex with a slightly elevated RS-T segment and a low upright T wave in Lead III. Although the QRS pattern in Leads II and III was suggestive of posterior infarct, the absence of serial changes in T_2 and T_3 left the diagnosis in doubt. However, the precordial leads taken during the first week showed a marked depression of the RS-T segment, maximal in Lead V_2 and comparable to that present in corresponding leads of the tracing of December 2 of Fig. 7 (Case 128). During the second week of hospitalization, the RS-T junction approached the isoelectric line and the R and T waves increased considerably in amplitude, especially in Lead V_2 ; this finding was comparable to that in the precordial leads of November 27 of Fig. 7. The changes in the precordial leads were typical of the reciprocal effects produced by recent posterolateral infarction. The electrocardiogram taken on his final admission revealed auricular fibrillation with numerous ventricular premature beats from multiple foci. The duration of the QRS complex in the beats of supraventricular origin was 0.12 second. The initial deflection of the supraventricular beats was upright in all precordial leads and in aV_L and aV_F . The R wave was coarsely slurred and prolonged in precordial leads over the left ventricle. This was interpreted as evidence of incomplete left bundle branch block. Lead aV_F displayed a small initial R wave followed by a broad, notched S wave. This was attributed to transmission of the potential variations of the epicardial surface of the posteroinferior aspect of the right ventricle to the left leg, as a result of horizontal position of the heart. Thus, Lead aV_F and the standard leads showed no evidence of the posterolateral infarct which had occurred seventeen months previously.

Pathologic Findings.—The heart weighed 655 grams and revealed a healed infarct occupying the posterolateral aspect of the basal two-thirds of the left ventricle. This infarct was comparable in position and size to that in the third, fourth, fifth, and sixth segments in Case 125 (Fig. 4). Microscopic examination revealed that the involvement was dense in the subendocardial one-third and patchy in the remainder of the wall. The posterior portion of the infarct was probably missed in Lead aV_F because of the horizontal position of the heart with transmission of potential variations of the posteroinferior surface of the right ventricle to the left leg. The infarction of the lateral wall was probably missed because of the incomplete left bundle branch block.

CASE 137.—An 87-year-old man was admitted to the hospital because of senile dementia complicated by bronchopneumonia. No past history was obtainable. Death occurred on the fourth hospital day from pneumonia.

Electrocardiographic Findings.—An electrocardiogram on the second hospital day showed auricular fibrillation. The QRS interval was within normal limits. Leads V_L , V_6 , and aV_L

displayed a tall, slurred, initial R wave, depressed RS-T junction, and shallow inversion of the T wave, interpreted as evidence of left ventricular hypertrophy. In Lead aV_F there was a slurred QS complex, 3.0 mm. in depth, followed by a low upright T wave. The question arose as to whether this was a remnant of an old posterior infarct or whether it was merely the result of transverse position and due to transmission of potential variations of the right ventricle to the left leg. The former alternative was preferred in the ante-mortem interpretation, but the patient's condition did not permit further investigation by means of esophageal leads and by repetition of Lead aV_F in different postures.

Pathologic Findings.—The heart weighed 508 grams and revealed an old, completely healed infarct confined to the posterolateral aspect of the left ventricle in the apical two segments. The lesion was comparable in position to that in the corresponding segments in Case 132 (Fig. 11), but was slightly smaller in size and was confined to the subendocardial one-half of the wall. The lateral portion of the infarct was not detectable in Leads V_6 , V_6 , and aV_L , probably because of the relatively small size of the lesion in comparison with the mass of uninfarcted hypertrophied lateral wall of the left ventricle. The QS complex in Lead aV_F , which had led to the ante-mortem diagnosis of posterior infarct, was probably not a manifestation of the posterior infarct found at autopsy because of the relatively small size and subendocardial location of the latter. It is more likely that this QS complex was due to transmission of the potential variations of the right ventricle to the left leg.

COMMENT

Interpretation of Lead aV_L .—When a QR or QS complex is recorded in Lead aV_L , determination of the cardiac position is an important prerequisite to the interpretation of the findings. This is accomplished through a study of the QRS pattern in the unipolar limb leads in reference to that in the precordial or other semidirect leads, as discussed in detail in a previous communication.¹¹ On the basis of the findings in Lead aV_F , the position of the heart in a given case can usually be classified into one of the following two groups: (a) horizontal to semihorizontal, and (b) vertical to intermediate. The cardiac position falls within the former range when Lead aV_F displays either (1) a small R and deep S wave, (2) an equiphasic RS complex, (3) an RSR' pattern, or (4) a QS pattern not due to extensive posterior infarction.⁸ The cardiac position falls within the latter range when Lead aV_F exhibits (1) a prominent R wave with a relatively small Q and/or S wave, (2) a monophasic upright deflection, and (3) an abnormal QR or QS pattern attributable to posterior infarction.⁸

(a) *Differentiation of the Normal and Abnormal QR Complexes in Lead aV_L in Horizontal to Semihorizontal Position of the Heart:* Under these circumstances, the potential variations of the left arm are transmitted principally from the epicardial surface of the free wall of the left ventricle. In the vast majority of the cases, especially when the apex is directed anteriorly, the lateral wall of the left ventricle faces toward the left arm and constitutes the main source of the QRS-T pattern recorded in Lead aV_L . In some cases, particularly when the apex is displaced backward, the basal aspect of the posterior or posterolateral wall may face toward the left arm and thus may exert the predominant effect upon the potential variations of the left arm.

The decision as to whether the potential variations of the left arm were transmitted chiefly from the lateral or from the posterobasal wall of the left ventricle was of some importance in the evaluation of borderline QR patterns

in Lead aV_L , because of the fact that the normal Q wave, registered through esophageal leads opposite the posterobasal wall of the left ventricle, is slightly longer in duration and slightly larger in proportion to the succeeding R wave than the normal Q wave registered through axillary leads opposite the lateral wall, because of the later onset of activation of the posterobasal wall. Thus, the normal Q wave in Leads V_5 , V_6 , and also in aV_L (if the potential variations of the left arm are transmitted chiefly from the lateral wall of the left ventricle) measures 0.02 second or less from onset to nadir, and is less than 25 per cent of the amplitude of the succeeding R wave. On the other hand, the normal Q wave in esophageal leads opposite the posterobasal wall of the left ventricle and also in aV_L (if the potential variations of the left arm are derived mainly from this portion of the heart) may reach 0.03 second in duration and may approach 25 per cent of the amplitude of the succeeding R wave.

Indirect evidence of the chief source of the QRS pattern in Lead aV_L may be obtained from (1) the direction of the associated P wave, provided sinus rhythm is present, and (2) the contour of the QRS complex in Lead aV_R . When the epicardial surface of the lateral wall of the left ventricle faces toward the left arm, the potential variations of the lower part of the lateral aspect of the left atrium are transmitted through the lateral wall of the left ventricle to the axilla and left arm, resulting in an upright P wave with gradually sloping limbs in Lead aV_L , resembling that in Leads V_5 and V_6 . Backward rotation of the heart favors transmission of the potential variations of more of the posterior wall of the left atrium to the left arm, resulting in a diphasic to inverted P wave with a steep downstroke, reminiscent of the diphasic to inverted P waves with prominent intrinsicoid downstroke registered through esophageal leads behind and above the left atrium.

When the heart is rotated on its transverse axis, so as to carry the apex backward and tilt the base upward, transmission of the potential variations of the posterobasal aspect of the left ventricle is prone to occur toward the right as well as the left arm, resulting in a prominent late R wave in Lead aV_L . Such a finding in Lead aV_R suggests, but does not necessarily imply, that an associated QR complex in Lead aV_L is derived from the potential variations of the posterobasal aspect of the left ventricle. On the other hand, the absence of this late R wave from Lead aV_R or the presence of a rudimentary late upstroke in this lead constitutes negative evidence suggesting that the QR complex in Lead aV_L was not derived from the posterobasal, but rather from the lateral, wall of the left ventricle.

A QR complex of 0.5 millivolt or more in Lead aV_L , transmitted from the epicardial surface of either the lateral, posterolateral, or posterobasal aspect of the left ventricle, may be considered abnormal and referable to infarction when (1) the time interval from onset to nadir of the Q wave is more than 0.03 second and the Q/R ratio exceeds 25 per cent, and (2) the Q wave is followed by an upstroke that is notched or coarsely slurred and consumes 0.05 second or more from onset to nadir. If the voltage of the QRS complex is below 0.5 millivolt, the Q/R ratio and the contour of the ascending limb of the R wave become less significant and the tracing is classed as borderline unless the time interval from

onset to nadir of the Q reaches 0.04 second or that from onset to peak of R reaches 0.06 second. The significance of QR complexes of 0.5 millivolt or more with a Q-wave duration of 0.02 to 0.03 second depends upon the portion of the heart chiefly responsible for the pattern in Lead aV_L . If Lead aV_L reflects the potential variations of the lateral wall of the left ventricle, these findings may be considered abnormal when accompanied by a Q/R ratio over 25 per cent; otherwise they may be considered borderline. If Lead aV_L reflects the potential variations of the posterobasal wall of the left ventricle, these findings may be considered borderline in the presence of a Q/R ratio above 25 per cent, and otherwise normal. A deep QS complex is a very rare finding in Lead aV_L of a semihorizontal to horizontal heart and would point to complete transmural infarction, provided one could be certain that the potential variations of the left arm were transmitted from the epicardial surface of the left ventricle and not from the mitral orifice, in the manner to be discussed.

(b) *Differentiation of the Normal and Abnormal QR Complexes in Lead aV_L in Vertical, Semivertical, or Intermediate Position of the Heart:* When the heart is in intermediate position, the epicardial surface of the lateral wall of the left ventricle generally faces toward the left arm. The derivation of the potential variations of the left arm is comparable to that when the heart is in horizontal to semihorizontal position and rotated so that the lateral aspect of the left ventricle is directed toward the left arm. The findings in Lead aV_L , both in the presence and absence of lateral infarction, and the criteria for the differentiation of the abnormal and normal QR complexes are consequently similar to those previously described.

Vertical to semivertical position of the heart is generally accompanied by sufficient clockwise rotation about the longitudinal axis so that the potential variations of the anterior wall of the right ventricle or anterior terminus of the septum are transmitted to the left arm. Under these circumstances, infarction of the lateral wall of the left ventricle is not detectable in Lead aV_L . The usual findings in this lead consist of either a small R and deep S wave, an equiphasic RS, or a multiphasic RSR' complex, resembling patterns in precordial leads over the right ventricle or at the transitional zone.

When vertical to semivertical position is accompanied by counterclockwise rotation, rather than the usual clockwise rotation about the longitudinal axis, the potential variations of the left ventricular cavity may be transmitted through the mitral orifice and left atrium to the left arm. As a consequence, Lead aV_L displays a deep and prolonged Q wave, representing negative potentials from the left ventricular cavity, usually followed by a late R wave, derived from activation of the posterobasal wall of the left ventricle.¹¹ The Q wave is large and the R wave small or absent, as in esophageal leads above the heart, when the predominant pathway to the left arm is through the roof of the left atrium, and the Q wave is less prolonged and less deep and the R wave taller, as in esophageal leads behind the left atrium, when the predominant pathway to the left arm is through the posterior wall of the left atrium. The QR or QS complex, which occurs as a normal variant in Lead aV_L in a semivertical to vertical heart, rotated counterclockwise on its longitudinal axis, may be identical with that which occurs

as a manifestation of lateral infarction in intermediate position of the heart. Differentiation may sometimes be made through indirect evidence furnished by (1) the QRS pattern in Lead aV_R , (2) the direction and contour of the P wave in Lead aV_L , and (3) the nature of the change in the pattern of the P wave and QRS complex in Lead aV_L when the tracing is repeated in a different position and during deep respiration. When the foregoing evidence is inconclusive, supplementary high precordial and axillary leads are indicated.

(1) The vertical position which leads to the transmission of cavity potentials to the left arm generally results in the registration of a comparable QR pattern in Lead aV_R from simultaneous transmission of cavity potentials to the right arm. Thus the RS complex in Lead aV_R in Case 129 was strongly against vertical position, but compatible with the presence of a lateral infarction.

(2) When sinus rhythm is present, the direction and contour of the P wave in Lead aV_L is of considerable indirect aid in determining whether a QR or QS complex is a manifestation of lateral infarction in an intermediate heart or a normal variant associated with vertical or semivertical position. The upright P wave with gently sloping limbs normally found in Leads V_5 and V_6 is due to transmission of the potential variations of the lower part of the left atrium through the lateral wall of the left ventricle to the electrode in the axilla. The registration of an upright P wave in Lead aV_L , which is similar to that in Leads V_5 and V_6 , indicates that the potential variations of the left atrium are likewise transmitted through the lateral wall of the left ventricle to the left arm. This constitutes strong indirect evidence that the predominant pathway for the transmission of the potential variations of the left ventricle to the left arm extends from the epicardial surface of the lateral wall and not from the cavity through the mitral orifice. A prolonged Q wave and high Q/R ratio in Lead aV_L , under these circumstances, are diagnostic of lateral infarction.

The inverted and diphasic P wave with precipitous intrinsicoid downstroke normally recorded in esophageal leads from above and behind the left atrium is due to direct transmission of the potential variations of the superior and posterior walls of the left atrium to the nearby electrode. The registration of an inverted to diphasic P wave with a steep downstroke in Lead aV_L indicates transmission of the potential variations of the superior or posterior walls of the left atrium directly to the left arm. When Lead aV_F displays a prominent R wave derived from the posterior wall of the left ventricle, the combination of an inverted to diphasic P wave and QR to QS complex in Lead aV_L suggests that the predominant pathway from the ventricles to the left arm may extend from the endocardial surface through the mitral orifice and left atrium. Under these circumstances, a deep, prolonged Q wave may be found in Lead aV_L , irrespective of the presence or absence of infarction of the free wall of the left ventricle. Further procedures essential to the differential diagnosis are discussed later.

(3) Repetition of Lead aV_L in the erect posture and during deep breathing is advisable when the tracing in the recumbent position reveals an inverted or diphasic P wave and a deep, prolonged Q wave. If such a maneuver produces an upright P wave in Lead aV_L , the nature of the change in the QRS pattern will aid considerably in determining whether the Q wave in the original tracing was

a normal variant or a manifestation of lateral infarction. Disappearance of the Q wave or drastic reduction in its duration to 0.02 second or less and in its amplitude to 25 per cent or less of the succeeding R wave indicates that the Q wave in the original tracing was a normal variant. Persistence of a Q wave over 0.02 second in duration and a Q/R ratio exceeding 25 per cent points toward lateral infarction, as will be exemplified by the findings in Case 142.

(4) Supplementary high precordial leads,¹² taken at the intersections of a horizontal line through the sternal terminus of the third intercostal space with vertical lines in the plane of precordial Positions 3, 4, 5, 6, and 7 are advisable whenever the findings in Lead aV_L are suggestive, but not diagnostic, of infarction. Discussion of these leads has been reserved for a companion manuscript on lateral infarction.⁹

Correlation of Electrocardiographic and Pathologic Findings in Posterolateral Infarction.—The thirty-three cases of posterolateral infarction were classified in accordance with the distribution of the lesion in reference to the long axis of the heart into the following groups: apical one-third, nine cases; middle one-third, one case; apical one-half to two-thirds, five cases; basal one-half to two-thirds, four cases; infarction extending more than two-thirds of the length of the posterolateral wall, fourteen cases. The infarct was confined to the subendocardial half of the wall in eight cases. In the remainder, it was most dense in this layer, but reached the epicardial surface of a portion of the posterolateral wall. The lesion was recent in twelve cases and healed in the other twenty-one. Electrocardiographic studies were made during the acute stage in four of the latter.

The standard leads are not reviewed since separate analyses have shown them inferior to the Goldberger leads in the detection of both posterior and lateral infarction.^{8,9} Precordial Leads V₁ through V₄ revealed reciprocal changes in the RS-T complex in eleven of the sixteen patients observed during the acute stage of posterolateral infarction. The presence of acute RS-T depression in these leads or the presence of exceptionally tall R or T waves is sufficient to arouse the suspicion of posterior or posterolateral infarction.

The evidence in Lead aV_F referable to the posterior portion of the infarct was interpreted in accordance with previously described criteria⁸ as either diagnostic, borderline to strongly suggestive, or negative. The signs in Leads aV_L, V₆, and V₅ referable to the lateral portion of the infarct were similarly interpreted, according to criteria already described. With these four leads being taken into consideration, the cases have been classified into the following four groups: (1) those with findings suggestive to diagnostic of both aspects of the infarct (ten cases); (2) those with signs of the lateral, but not the posterior, lesion (nine cases); (3) those with evidence of posterior, but not of lateral, infarction (twelve cases); and (4) those with negative findings (two cases).

(1) Leads V₅, V₆, aV_L, and aV_F supplied evidence regarded as diagnostic of both the lateral and posterior aspects of the recent lesion in Cases 124, 126, and 130, and of both aspects of the healed infarct in Cases 96, 129, and 131. The QR pattern was borderline in Case 130 and the diagnosis was established by the associated changes in the RS-T complex. In Case 126, signs of the lateral extension were present in Lead V₆ during the acute stage, but disappeared after

the lesion healed. Evidence diagnostic of the lateral and suggestive of the posterior part of the infarct was found in two other patients with a recent lesion (Cases 125 and 127) and one with a healed lesion (Case 132), and signs suggestive of both parts of the old infarct, but diagnostic of neither, were found in Case 133. In most of the patients with abnormal Q-wave patterns in Leads V_5 and V_6 , the lesion continued into the apical third of the anterolateral wall. Occasionally, as in Case 124, abnormal Q waves were found in Lead V_6 and even in Lead V_5 , despite the fact that the anterior boundary of the lesion was in the posterior part of the lateral wall. Counterclockwise rotation, together with forward displacement of the apex, probably accounted for the transmission of the potential variations of the infarcted posterolateral wall of the apex to Positions 5 and 6.

(2) The electrocardiogram was strongly suggestive to diagnostic of the lateral portion of the infarct, but negative for the posterior part of the infarct in three patients with a recent lesion and in six with a healed lesion. The absence of signs from Lead aV_F was attributable to horizontal position in five patients (Cases 135, 151, 152, 154, and 159); and to a primary lateral infarct, which involved only the apical third of the posterolateral wall, in three (Cases 142, 145, and 157). Extensive lateral and posterolateral infarction was present in the remaining patient (Case 158), and the normal pattern in Lead aV_F was probably transmitted from the intact posteroseptal portion of the wall.

(3) The electrocardiogram was strongly suggestive to diagnostic of the posterior portion of the infarct, but failed to show QRS changes of lateral infarction in Cases 19, 87, 88, 93, 94, 104, and 128, studied in the acute stage, and in Cases 95, 97, 98, 100, and 134, studied after healing. RS-T patterns suggestive of the ischemic zone were found in Leads V_5 , V_6 , and/or aV_L in six of the seven patients with a recent posterolateral infarct.

The lesion involved the apical portion of the posterolateral wall in Cases 93, 94, and 100. Incomplete left bundle branch block accounted for the absence of diagnostic signs in Leads V_5 , V_6 , and aV_L in Case 100. The findings were negative in the other two patients, despite the fact that the infarct continued into the apical portion of the anterolateral wall. This was explained by the presence of marked clockwise rotation. In Case 93, all three leads reflected the potential variations of the transitional zone, whereas in Case 94, Lead V_5 was transitional and Leads V_6 and aV_L reflected the potential variations of the anteroseptal wall of the left ventricle.

Extensive infarction of the basal two-thirds of the posterolateral wall was found in Cases 19, 87, 88, 95, 97, 98, 104, 128, and 134. The failure to detect signs of the lateral portion of the lesion in Lead aV_L of seven of these patients was due to clockwise rotation. The pattern in Lead aV_L of these patients corresponded closely with that in one of the first four precordial leads, indicating that the potential variations of the left arm were transmitted chiefly from the anteroseptal wall of the right or left ventricle. The prominent R wave found in Lead aV_L of the other two patients (Cases 87 and 88) was representative of the pattern customarily attributed to transmission of the potential variations of the lateral wall of the left ventricle to the left arm. This R wave resembled that recorded in Leads V_4 through V_6 and was probably derived from the uninfarcted

anteroseptal wall or apical third of the anterolateral wall. The infarct continued into the apical portion of the posterolateral wall of most of the foregoing nine patients, but failed to involve the apical third of the anterolateral wall. The sparing of this portion of the heart, together with the clockwise rotation, accounted for the absence of abnormal Q-wave patterns in Leads V_5 and V_6 .

(4) Neither aspect of the infarct was diagnosed from the standard and unipolar limb leads and precordial Leads V_1 through V_6 in Cases 136 and 137. The failure to recognize the posterior part of the lesion was attributable to horizontal position in both cases. Left bundle branch block obscured signs of the lateral infarct in Case 136. The lesion of the lateral wall was relatively small in Case 137, but might have been recognized, if additional leads had been taken.

From a survey of these and other cases, it would appear that abnormal Q-wave patterns are usually present in Leads V_5 and/or V_6 when the infarct involves the apical third of the anterolateral wall, but not when it involves the apical third of the posterolateral aspect of the left ventricle. Leads V_7 and V_8 may provide evidence of the latter,¹ and should be taken when the routine leads reveal changes suggestive of either posterior or lateral infarction. Extensive infarcts of the basal one-half or two-thirds of the posterolateral wall are not recognizable from Lead aV_L when there is sufficient clockwise rotation so that the pattern in this lead resembles that in one of the first four precordial leads. Under these circumstances, high precordial and axillary leads are indicated and are preferably taken at the intersections of a horizontal line at the level of the sternal terminus of the third intercostal space with vertical lines in the plane of the V_4 through V_7 positions. The posterior portion of an extensive posterolateral infarct is not detectable in Lead aV_F when the heart is rotated counterclockwise into a semihorizontal to horizontal position. If leads in the posterior axillary line are negative or inconclusive in horizontally placed hearts, esophageal leads may be needed to establish or exclude posterior infarction.

SUMMARY

In thirty-three cases of pathologically established posterolateral infarction, electrocardiograms consisting of precordial Leads V_1 through V_6 and the Goldberger and standard limb leads were studied to evaluate the evidence furnished by these leads for the detection and localization of the infarct. The findings in Lead aV_F were employed as an index of the posterior aspect of the lesion and the findings in Leads V_5 , V_6 , and aV_L were used as an index of the lateral aspect. The interpretation of Lead aV_L has been discussed in detail, whereas the criteria used for the other leads were established in previous reports.

In eleven of the sixteen patients observed during the acute stage, precordial Leads V_1 through V_4 revealed reciprocal depression of the RS-T segment or exaggeration in the height of the R and/or T waves, sufficient to arouse the suspicion of posterolateral infarction. On the other hand, the standard limb leads were much less dependable than the unipolar limb leads and supplied no additional information.

The findings in Leads aV_F , aV_L , V_5 , and V_6 were regarded as strongly suggestive to diagnostic of both aspects of the infarct in ten cases; of the posterior, but not the lateral, lesion in nine cases; of the lateral, but not the posterior, lesion in twelve cases; and were negative in the other two cases.

The commonest cause for failure to detect the posterior portion of the infarct in Lead aV_F was counterclockwise rotation into a semihorizontal to horizontal position. However, lesions that involved the posterolateral, but spared the posteroseptal, wall were sometimes not recognizable from Lead aV_F , even though the heart was in a vertical to intermediate position.

The commonest cause for failure to detect evidence of posterolateral infarction in Lead aV_L was clockwise rotation. In nine patients with extensive infarction of the basal portion of the posterolateral wall, the QRS pattern in Lead aV_L resembled that in one of the first four precordial leads, indicating that the potential variations of the left arm were transmitted chiefly from the antero-septal wall of the right or left ventricle.

Leads V_5 and V_6 seldom yielded abnormal Q-wave patterns unless the posterolateral infarct continued into the apical third of the anterolateral wall. The occasional association of abnormal Q-wave patterns in Lead V_6 or both Leads V_6 and V_5 with infarction of the apical third of the posterolateral wall was attributed to counterclockwise rotation of the heart or anterior displacement of the apex.

Precordial Leads V_1 through V_6 , together with the Goldberger and standard limb leads, are inadequate for the accurate localization of posterolateral infarction, but generally reveal sufficient evidence to arouse the suspicion of at least one aspect of the lesion. Under these circumstances, Leads V_7 , V_8 , and supplementary high axillary leads are indicated to explore the apical and basal aspects, respectively, of the posterolateral wall.

REFERENCES

1. Wilson, F. N., et al.: Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
2. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, *Advances in Internal Medicine* 2:1, New York, 1947, Interscience Publishers.
3. Hecht, H. H.: The Localization of Myocardial Infarcts With Particular Reference to Lateral Infarction and the T_1Q_3 Pattern, *Proc. Am. Federation Clin. Research* 2:102, 1945.
4. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Anteroposterior Infarction, *AM. HEART J.* 37:205, 1949.
5. Goldberger, E.: The Differentiation of Normal From Abnormal Q Waves, *AM. HEART J.* 30:341, 1945.
6. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Large Anterolateral Infarcts, *AM. HEART J.* 36:838, 1948.
7. Myers, G. B., and Oren, B. G.: The Use of the Augmented Unipolar Left Leg Lead in the Differentiation of the Normal from Abnormal Q Wave in Standard Lead III, *AM. HEART J.* 29:708, 1945.
8. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Posterior Infarction, *AM. HEART J.* In press.
9. Myers, G. B., Klein, H. A., and Stofer, B. E.: Correlation of Electrocardiographic and Pathologic Findings in Lateral Infarction, *AM. HEART J.* 37:374, 1949.
10. Myers, G. B., Klein, H. A., and Stofer, B. E.: Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction, *AM. HEART J.* 36:535, 1948.
11. Myers, G. B., and Klein, H. A.: The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads, *AM. HEART J.* 35:727, 1948.
12. Rosenbaum, F. F., Wilson, F. N., and Johnston, F. D.: The Precordial Electrocardiogram in High Lateral Myocardial Infarction, *AM. HEART J.* 32:135, 1946.

THE PULMONARY ARTERIAL PRESSURE

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IN THE course of an analysis of factors involved in the maintenance of the normal systemic arterial pressure^{1,2} we became interested in certain comparative aspects of the pulmonary arterial pressure. For this purpose we have measured the pulmonary arterial pressure in a reptile (turtle) and a bird (chicken) and we have reviewed data previously obtained in a mammal (dog).^{3,4,5} These studies suggest that while the systemic arterial pressures may vary widely in the various classes, the pulmonary arterial pressures are remarkably similar in all vertebrates.

METHODS AND RESULTS

Turtle.—Pulmonary and systemic arterial pressures were measured in fourteen turtles (*Pseudemys elegans*) after removal of a circular disc, about 3.0 cm. in diameter, from the plastron overlying the heart and great vessels. The subjacent connective tissue was stripped away to expose the left pulmonary artery and the left aorta. The pressure in the main pulmonary artery was measured with a cannula introduced cardiad into the left pulmonary artery. The systemic pressure as transmitted via the right aorta was determined by means of a second cannula placed peripherad into the left aorta. The cannulas were then attached to the Hamilton manometers⁶ for optical registration of the pressure pulses. Heparin was used to prevent clotting.

During ventricular systole the pressures in the pulmonary artery and in the aorta reached essentially similar levels. During diastole, the pulmonary pressure fell away more rapidly and to lower levels than did the aortic. As a result, the pressure in the pulmonary artery at the end of diastole was usually from 10 to 30 mm. Hg lower than that in the aorta. Because of this lower pressure, ejection and the rise in pressure began earlier during the following contraction of the common ventricle in the pulmonary than in the systemic vessels.

The pulse pressure in the systemic circuit was 5 to 10 mm. Hg less than that in the pulmonary artery (Table I) and it was relatively constant and independent of the height of the systemic pressure. For example, in the course of one given experiment, pressures of 35/27 and 19/10 mm. Hg were recorded at separate times.

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Aided in part by a grant from the Department of the Army to the Michael Reese Hospital (Dr. L. N. Katz, the responsible investigator).

TABLE I. PULMONARY AND AORTIC PRESSURES IN THE TURTLE

TURTLE NUMBER	AORTIC PRESSURE*		PULMONARY ARTERIAL PRESSURE	
	SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)	SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)
158	42	28	40	10
159	41	29	40	24
160	30	22	30	10
161	30	25	32	8
162	—	—	30	10
174	37	28	35	10
AVERAGES	36	26	35	12

*In this column, — means no record made.

By contrast, the pulmonary pulse pressure was much more variable. The pulmonary diastolic level was almost always below 20 mm. Hg, ranging between 8 and 24 mm. Hg, and averaging about 12 mm. Hg (Table I). Conditions which tended to raise the systemic pressure reflected themselves in the pulmonary circuit primarily by an increase in the *systolic* pressure, but had only a slight effect on the diastolic level. For example, warming the turtle, or the injection of epinephrine, usually elevated the systemic diastolic pressure and the systolic pressures in both circuits by the same amount, but the pulmonary diastolic pressure was little affected.

Dog.—This laboratory has previously used a modified London cannula to measure the pulmonary arterial pressure in the intact unanesthetized dog.^{4,5} These experiments have shown the pulmonary arterial pressure to range about 28–40 mm. of mercury. This value was not affected by the induction of systemic nephrogenic hypertension,⁴ nor by epinephrine and acetylcholine, agents which markedly affected the systemic pressure.⁵ The pulmonary arterial pressure appeared to be affected almost solely by a disparity in the output of the left and right ventricles, thus responding passively, rather than actively, as is the case in the systemic circuit. These results are similar to those of other investigators in the cat⁷ and in man.

Chicken.—The pulmonary arterial pressure was measured successfully in six white Leghorn chickens of about 16 weeks of age. The pentobarbitalized animal was placed on its right side and the left wing folded back to expose the thoracic cage. The prominent external thoracic vein can be seen coursing from the angle of the wing in a posteroventral direction. An incision about 2 inches in length was made along this vein, exposing the pectoralis major, which was then separated from the thoracic cage by blunt dissection. The sternal portions of the ribs were removed and the pericardial sac was split, exposing the left pulmonary artery. This vessel was then ligated as close to the lung hilum as possible and cannulated. Much care was necessary at this point because of the fragility of the vessel, especially in young birds. The cannula was attached to the optically recording Hamilton manometer. A typical record is illustrated in Fig. 1.

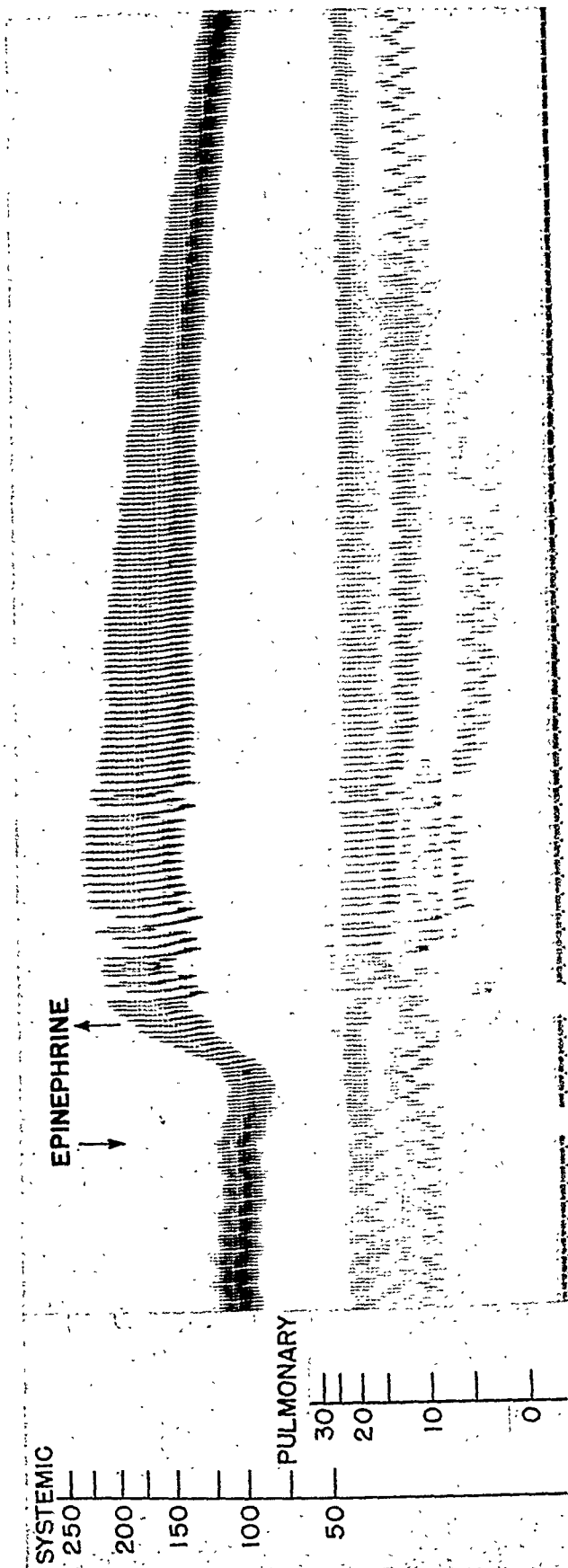


Fig. 1.—The pulmonary and arterial blood pressure in the chicken. Effect of 0.5 mg. of epinephrine. Calibrated in mm. of mercury. Upper curve, systemic arterial pressure. Lower curve, pulmonary arterial pressure. Epinephrine injection given between the arrows. Time is in seconds. Note that epinephrine injection produced a slowing of the heart which was associated with an increase in the systemic arterial pressure, but with no significant change in the mean pulmonary arterial pressure.

The normal pulmonary arterial pressure of the chicken was found to average 23-12 mm. Hg, ranging from 15 to 30 systolic and from 5 to 20 diastolic (Table II). The possibility that the opening of the thorax or the occlusion of the left pulmonary artery may have introduced errors into the measurement must be mentioned. Obstruction of the left pulmonary artery would, if anything, have tended to increase the pulmonary arterial pressure. However, results on animals, including man, show that neither opening of the pleura to atmospheric pressure nor occlusion of one major branch of the pulmonary artery significantly alters the pressure in the main pulmonary artery.⁷

TABLE II. PULMONARY ARTERIAL PRESSURE IN THE CHICKEN

CHICKEN NUMBER	SYSTOLIC PRESSURE (MM. Hg)	DIASTOLIC PRESSURE (MM. Hg)	HEART RATE (PER MINUTE)	RESPIRATORY RATE* (PER MINUTE)
1	32	20	276	60
2	26	10	260	36
3	18	7	380	48
4	18	8	240	—
5	31	20	282	48
6	17	10	318	51
Averages	24	12	293	49

*In this column, — means no record made.

The systemic blood pressure, recorded from the sciatic artery ranged from 130/100 to 90/75 mm. of mercury. These values, lower than those found in unanesthetized intact birds,¹ may have been the result of the trauma produced by the surgery or of the action of the anesthetic on the circulation and on body temperature.

Injection of 1.0 mg. of epinephrine into the sciatic vein resulted in a rise in systemic pressure of 40 to 80 mm. Hg; the pulmonary arterial pressure was affected only slightly with occasional rises of up to 5.0 mm. Hg followed by a fall of this magnitude (Fig. 1). As in the dog, these appeared to represent passive changes resulting from changes in heart rate and backward transmission of the effect of the vasoconstrictor agent on the systemic circuit and from variations in venous return during recovery from systemic vasoconstriction.

DISCUSSION

The fact that the pressure in the artery to the respiratory apparatus (respiratory arterial pressure) is essentially of the same order in three different classes of vertebrates suggested that it would be of value to consider more generally some comparative aspects of the lesser circulation. These are represented schematically in Fig. 2. Only physiological situations are discussed; pathological variations will be taken up in a later communication.

The functional equivalent of the pulmonary circulation in the fish is seen in the gill circulation, in which the process of oxygenation of the blood and loss of

carbon dioxide is accomplished. The few blood pressures which have been recorded in the fish show the pressure to be about 30 mm. Hg in the ventral aorta (pulmonary) and about 23 mm. Hg in the dorsal aorta (systemic).⁸⁻¹² In the passage of the blood through the low-resistance gill capillaries and the collection of the oxygenated blood into the dorsal aorta, the pressure is necessarily somewhat reduced. The gill capillaries apparently impose little resistance to flow.⁸ In this primitive type of cardiovascular system, the pressure in the ventral aorta (respiratory) is slightly higher than that in the systemic circu-

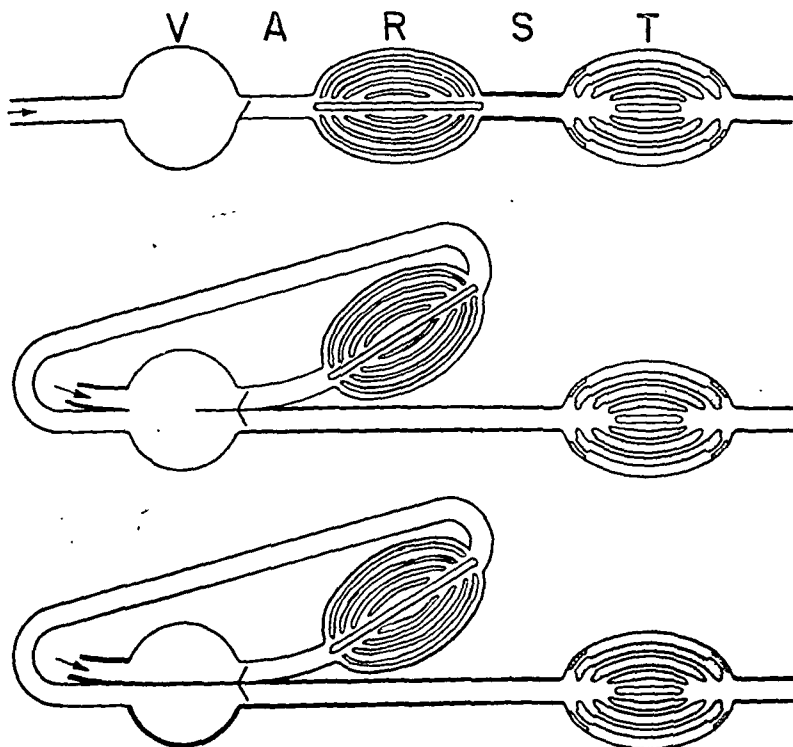


Fig. 2.—A schematic representation of the relation between the pulmonary and systemic pressures in the fish (upper diagram), amphibiae and reptiles (middle diagram), and mammals and birds (lower diagram). At the left, the arrow indicates the route of the venous return from the systemic circuit. Under V is placed the ventricle(s); under A is the artery to the respiratory organ; under R is the respiratory organ, either gill or lung; under S is represented the systemic aorta; and under T is placed the systemic organs with various types of vasomotor action in the several parallel circuits. The design of R suggests the low-resistance circuit of the homogeneous respiratory organ. The design of T suggests the means by which blood is redistributed to heterogenous parts of the systemic circuit. Low-resistance shunts (center) are parallel with progressively vasoactive shunts and a sinusoid-type shunt at the periphery.

lation represented by the dorsal aortas (Fig. 2). Irving¹¹ remarks that perfusion pressures higher than 35 mm. Hg were not practicable since the thin-walled ventral aorta distended excessively under such abnormal conditions. As a result of its position in the vascular tree, the respiratory organ is thus seen as a limiting factor in the level of the systemic pressure which can be attained in the fish.

The next major step in the evolution of the respiratory equipment is exemplified in the development of the pulmonary and cutaneous vasculature in the amphibiae. The systemic arterial pressure has been measured in these

animals and found to be of the same order as that seen in the turtle for the same body temperature.^{13,14} The general similarity of the circulation in the amphibiae and the reptiles makes it likely that their circulations operate on similar principles. In the reptiles, the cutaneous respiratory circulation is lost, and the interventricular septum is better developed, but the ventricle still acts essentially as a single chamber. The systemic and pulmonary *systolic* pressures are equal. However, the diastolic pressure in the systemic circuit is definitely higher than in the pulmonary system. As a result, the *mean* systemic pressure is placed at higher levels than the mean pulmonary pressure. This is accomplished by the action of the spiral valve in the pulmonic-aortic trunk which, during diastole, prevents the regurgitation of blood from the higher pressure of the systemic circuit into the pulmonary artery.

Minor adjustments in the output through the systemic and pulmonary circuit may occur since Woodbury and Robertson¹⁵ have suggested that after hemorrhage the orifice of the pulmonary artery may be closed during the greater part of systole. This may effectively reduce the pulmonary output and divert more blood to the systemic circuit. Despite this, the maximal pressure generated in the systemic circuit is still limited by the fact that ejection of blood from a single ventricle cannot effectively increase the systemic output without increasing the pulmonary output to an even greater extent. An increase in the systolic pressure must therefore result in a greater diversion of blood into the pulmonary circuit and cannot but contribute to a decreased efficiency of the heart beat as far as the systemic pumping action is concerned. At higher body temperatures and therefore at higher oxygen need, an increasing systolic pressure probably would act to increase the pulmonary flow at a greater rate than that being supplied to the aorta. In this way, the small respiratory surface area of the amphibian and reptilian lung may be partially compensated.

An interesting problem which has faced physiologists interested in the pulmonary circulation has been the remarkable *insensitivity* of the pulmonary circulation to the action of agents which markedly affect the systemic circuit. A plausible explanation of this unexpected refractoriness of the pulmonary vasculature may lie in its phylogenetic derivation and in the homogeneity of its structure. Thus it can be easily appreciated that in the fish an increase in resistance in the gill arterioles would markedly increase the work of the heart, but would provide no useful function in the gill circuit, since, if valuable filtrable elements of the plasma are not to be lost into the surrounding medium, the pressure must be reduced to levels which do not force a transudate through the respiratory capillaries. The utility of vasoactive substances and vasomotor reflexes apparently lies in the redistribution of blood flow from one to another portion of the heterogeneous systemic circuit. Thus muscular activity leads to vasodilation of the arterioles of the muscles and a consequent increase in blood flow to the active parts. Compensatory vasoconstriction in other parts of the systemic circuit occurs and prevents the fall in blood pressure which otherwise would develop. The homogeneity of the pulmonary circuit would appear to require no preferential shunting of blood in the lungs. In this system, the presence of active arterioles could act only to increase the load on the ventricle without accomplishing any useful function.

In the case of the common ventricle of the amphibiae and reptiles, pulmonary arteriolar vasoconstriction could act only to decrease the blood flow through the lungs and handicap the gaseous exchange in the lungs and lead toward anoxemia.

The division of the reptilian single-chambered ventricle into two separate chambers occurs in the homeothermic mammals and birds and accomplishes the separation of the arterialized from the venous blood. Of equal importance, it makes possible an increase in the systemic pressure without an equal increase in the pulmonary pressure.

The fact that at least three different groups of reptiles have developed a four-chambered heart has made it possible to compare certain features of the circulation and draw some general conclusions. The crocodiles apparently have maintained the pressure relationship seen in the turtle, with systemic pressures essentially of the same order as those in the lower reptiles.¹⁶ The presence of a large ductus arteriosus in these animals makes it likely that the pulmonary pressure is at similarly low levels. Mammals and birds, evolving from widely separated reptilian forebears, have developed body temperatures and systemic arterial pressures at different levels,¹⁷ but have evidently proceeded in a generally similar manner with regard to the level of the pulmonary arterial pressure. In mammals, body temperatures range about 37°C. with systemic diastolic pressures of about 80 mm. of mercury. Birds, with body temperatures about 42°C., have systemic diastolic pressures of about 120 mm. of mercury.¹⁰ However, the pulmonary arterial pressures in both groups of animals are about 25/10 mm. Hg, and this level, of course, is generally similar to that found in the pulmonary artery in the cold-blooded vertebrates.

The course of development of the circulation in the vertebrates is thus seen to involve the escape of the systemic circulation from the limitations placed upon it by the low-resistance pulmonary circuit. In the fish these circuits are in series, with the respiratory apparatus between the single ventricle heart and the systemic circulation. The assumption of terrestrial life was unquestionably facilitated by the development of the systemic circulation parallel with the pulmonic (Fig. 2), which permitted a significant but limited increase in the mean systemic pressure.

The cutaneous respiratory circulation is lost in the reptiles, but the incomplete separation of the ventricles marks no fundamental hemodynamic change. Similarly, the incomplete separation of the circulations seen in the crocodilia and in prenatal mammals and birds places limitations on the level to which the systemic pressure can be raised because of the low-resistance pulmonary shunt. The complete division of the ventricles in the homeotherms eliminates this effect and permits the systemic pressure to be raised independently of the pressure in the respiratory circuit. The final disappearance of shunts between the venous and arterial circulations (ductus arteriosus and foramen ovale) provides the pumping equipment for the increase in blood pressure without undue loss of efficiency of the heart, and makes possible a vascular apparatus capable of meeting the increased circulatory demands placed by the high metabolic rates of warm-blooded animals.

Probably the most significant factor limiting the level of the pulmonary arterial pressure is the low resistance to flow of blood through the respiratory apparatus. This in turn depends on the primary function of the respiratory

capillaries, which is the exchange of gases with the environment. Such capillaries, if they are to permit the rapid passage of oxygen and carbon dioxide, must be thin and in close contact with the external environment. For greatest efficiency they require a rapid flow of blood and a large surface area exposed to the environment. Further, the pressure must be lower than the oncotic pressure of the blood so that no significant transudate is produced. These conditions all conspire to maintain a low pulmonary arterial pressure.

The marked distensibility of the pulmonary capillaries, surrounded by air and unsupported by tissues, permits large increases in volume and thus prevents a significant pressure change during ventricular ejection. The fact that the mean pulmonary arterial pressure is probably only about 14 mm. Hg and the capillary pressure, about 10 mm. Hg makes possible the osmotic reabsorption during diastole of transudate which might pass through the capillary wall during the momentary heightened pressure of systole.

By their tremendous distensibility, the pulmonary capillaries furnish a buffer between right and left ventricles. Thus, the output of the left ventricle may, for brief periods, be less than the output of the right ventricle. No increased pulmonary pressure and, therefore, no increased transudate and edema occur until the storage capacity of the lungs, as indicated by a markedly reduced vital capacity, is encroached upon.

If the respiratory arterial pressure were to be raised significantly, the respiratory capillary epithelium would begin to function in a fashion similar to that of the renal glomerulus. In the fish this would lead to rapid dehydration and salt loss, while in the terrestrial animal, the accumulation of transudate on the pulmonary epithelium would impede gas diffusion and produce hypoxia, or if severe, would lead to frank pulmonary edema. In any event, the development of conditions permitting a significant increase in the respiratory capillary pressure would act as a lethal variant.

By contrast, the systemic capillaries are supported and surrounded by the tissues, and the production of transudate by an increased pressure automatically increases the tissue pressure and results in an increased return of such fluid to the circulation via the venous system or the lymphatics.

The respiratory arterial pressure is thus seen to be conservative throughout its history. On the other hand, the metabolic demands for an increased perfusion of the highly active tissues of the homeotherms have been met by the production of a higher head of pressure in the systemic circuit which was made possible by the escape of the systemic circuit from the pressure limitations placed upon it by the pulmonary circuit. However, this development opened the way for an unbridled increase in the level of the systemic arterial pressure which in some cases may be more than can be borne without injury to the heart and the vascular tree.

SUMMARY

Measurements of the systemic and pulmonary arterial pressure in a reptile (turtle), mammal (dog), and bird (chicken) were used as a basis for a study of the comparative physiology of the lesser circuit. Data on the ventral aortic (pul-

monary) pressure in the fish were available in the literature. In all these the pulmonary arterial pressure was low, ranging around 25/10mm. of mercury. However, the systemic arterial pressure varies markedly from class to class. In the fish, the systemic pressure is lower than that in the gill arteries. In the turtle, the systolic pressures are equal in both circuits, but the systemic diastolic is higher than the pulmonic diastolic pressure; therefore, the mean systemic pressure is also higher. In the homeotherms, the systemic pressure is much higher than in the pulmonary circuit.

The pulmonary arterial pressure remains low in the higher vertebrates, probably as a result of factors which act to increase the rate of exchange of blood gases with those of the environment. These include: (a) the enormous pulmonary vascular bed, (b) the absence of tissue support of the pulmonary capillaries which are exposed over nearly their entire surface to the environment, resulting in (c) the great distensibility of the capillaries permitting little increment in pressure with greatly increased volume. An increased pressure in such a capillary would produce a transudate and result in disturbed respiratory function.

The complete division of the primitive ventricle into two chambers resulted not only in the separation of arterial from venous blood, but also provided conditions in which the systemic pressure could be raised without directly affecting the pulmonary blood pressure and blood flow.

We wish to acknowledge our indebtedness to Dr. A. Surtshin and to Miss L. Taylor for technical assistance in the early phases of this study.

REFERENCES

1. Rodbard, S., and Tolpin, M.: A Relationship Between Body Temperature and the Blood Pressure in the Chicken, *Am. J. Physiol.* **151**:509, 1947.
2. Surtshin, A., Rodbard, S., and Katz, L. N.: Inhibition of Epinephrine Action in Severe Hypoxemia, *Am. J. Physiol.* **152**:623, 1948.
3. Johnson, V., Hamilton, W. F., Katz, L. N., and Weinstein, W.: Studies on the Dynamics of the Pulmonary Circulation, *Am. J. Physiol.* **120**:624, 1937.
4. Katz, L. N., and Steinitz, F.: Pulmonary Arterial Pressure in Experimental Renal Hypertension, *Am. J. Physiol.* **128**:433, 1940.
5. Katz, L. N., and Friedberg, L.: The Effect of Drugs on the Pulmonary and Systemic Arterial Pressure in the Trained Unanesthetized Dog, *J. Pharmacol. & Exper. Therap.* **77**:80, 1943.
6. Hamilton, W. F., Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal, *Am. J. Physiol.* **107**:427, 1934.
7. Alberti, V. A. J.: *La Presion de la Arteria Pulmonar*, Buenos Aires, 1948, El Ateneo.
8. Schoenlein, V., and Willem, K.: Beobachtungen über Blutkreislauf und Respiration bei einigen Fischen, *Ztschr. f. Biol.* **32**:511, 1895.
9. Bruenings, W.: Zur Kreislaufs der Fische, *Arch. f. d. ges. Physiol.* **75**:599, 1899.
10. Woodbury, R. A., and Hamilton, W. F.: Blood Pressure Studies in Small Animals, *Am. J. Physiol.* **119**:663, 1937.
11. Irving, L., Solandt, D. Y., and Solandt, O. M.: Nerve Impulses From Branchial Pressure Receptors in the Dogfish, *J. Physiol.* **84**:187, 1935.
12. Burger, J. W., and Bradley, S. E.: Some Data on Aortic Blood Pressures in the Dogfish, *Squalus acanthias*, *Anat. Rec.* **99**:670, 1947.
13. Schulz, F. N.: Studien über das Verhalten des Blutdrucks von *Rana esculenta* unter den verschiedenen aussern Bedingungen, insbesondere bei verschiedener Körpertemperatur, *Arch. f. d. ges. Physiol.* **115**:386, 1906.
14. Rodbard, S.: Unpublished data.
15. Woodbury, R. A., and Robertson, G. G.: The One Ventricle Pump and the Pulmonary Arterial Pressure of the Turtle, *Am. J. Physiol.* **137**:628, 1942.
16. Soetbeer: Quoted in Schulz.¹³
17. Rodbard, S.: Body Temperature, Blood Pressure, and Hypothalamus, *Science* **108**:413, 1948.

PLASMA HEXOSAMINE LEVELS IN ACUTE RHEUMATIC FEVER

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IN HUMAN plasma there is present a substance which has many of the properties of a polysaccharide. Present evidence, in part based on the work of Rimington,¹ of Bierry,² and of Hewitt,³ suggests that this material is composed of three sugars, mannose, galactose, and glucosamine, and further, that this polysaccharide is chemically bound to the various globulins and to some fractions of the albumin. This polysaccharide appears to be present in plasma concentrations of about 300 mg. per cent. The relatively high concentration, coupled with the fact that plasma polysaccharide has been reported to increase in a wide diversity of pathologic conditions, indicates that it may play an important role in human physiology. Nothing, however, is known about its function, origin, or fate.

No method is available for the direct determination of this substance. Various methods have been developed for estimating the total polysaccharide by the determination of one or more of its components, and the colorimetric methods of Tillmans and Philippi⁴ and of Elson and Morgan⁵ have had widest application. In the former, mannose and galactose are determined, and in the latter, hexosamine.* One of the limitations of the methods now in use is the uncertainty regarding the quantitative relation of these sugars to the total plasma polysaccharide. A second limitation is that these are colorimetric methods which depend on chemical reactions, the nature of which is still unknown.

Several observers have demonstrated that alterations take place in plasma polysaccharide levels in disease states. West and Clarke⁶ made a survey of serum hexosamine levels in a wide variety of conditions and reported values elevated above the normal in sera of patients with infectious diseases, malignancies, and sterile infarcts. In the course of their study they examined single samples of serum of seven patients with rheumatic fever and found that the serum hexosamine ranged from 125 to 184 mg. per cent, while the values determined in twenty-one normal individuals were 76 to 110 mg. per cent.

It has long been known^{7,8} that if the sera of patients with pneumonia were inoculated with pneumococci and then incubated, a precipitate appeared.

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This work was made possible in part by funds provided by the Committee for the Promotion of Medical Research, Inc.

*The term "hexosamine" refers here to the naturally occurring amino sugars, glucosamine and galactosamine. Since the methods currently in use fail to distinguish between these two, the more general term hexosamine is used.

whereas in sera of normal persons either no precipitate or only a faint turbidity resulted. Friedemann and Sutliff⁹ concluded, as a result of acid titration studies, that it was the presence of an increased amount of polysaccharide that was responsible for this phenomenon and that the increased lactic acid formation that resulted from fermentation of this polysaccharide precipitated the plasma proteins. They further concluded that this polysaccharide present in patients with pneumonia was fermented by pneumococci and thereby differed from the polysaccharide normally present which was not metabolized by the microorganisms. In addition, they were able to demonstrate that this phenomenon was not restricted to patients with pneumonia, but also could be shown to occur in sera of patients with other acute infections, with tuberculosis, and during the course of many normal pregnancies. Youngner,¹⁰ using this method of pneumococcal fermentation and resultant precipitate formation for estimating the amount of polysaccharide present, concluded that there was a relationship between the erythrocyte sedimentation rate and plasma polysaccharide levels in a group of diseases studied. This group included rheumatic fever, tuberculosis, pneumonia, malignancies, and coronary occlusion. Seibert and associates,^{11,12} studying individuals with tuberculosis, determined polysaccharide levels and electrophoretic plasma protein patterns. The increase in gamma globulin seen in minimal tuberculosis they felt was indicative of antibody formation, but the rise in the α_2 globulin and polysaccharide that occurred in advanced tuberculosis and carcinoma they suggested might represent tissue destruction.

It is apparent, then, that several workers have observed an increase in the polysaccharide in a wide variety of diseases. It seemed worth extending the investigation of West and Clarke to include a series of successive observations on plasma hexosamine levels in individual patients with rheumatic fever from the onset of the acute phase through the period of convalescence. In this manner, one might determine whether there were any similarity in the pattern demonstrated by different individuals with rheumatic fever, whether or not there were any relationship between the degree of polysaccharide elevation and the severity of the disease, and last, whether there were any correlation between the polysaccharide level and the erythrocyte sedimentation rate.

MATERIAL AND METHODS

The patients with active rheumatic fever reported herein were hospitalized either on the Third Medical Service or the Pediatric Service of Bellevue Hospital.

The seventy-six individuals whose hexosamine levels were taken to represent the normal range included thirty-five who were attending a follow-up cardiac clinic and were being treated for either potential, or possible and potential heart disease. None were included in whom there was any question of recent rheumatic activity. The remaining forty-one normal subjects included students, laboratory technicians, well children who were in the hospital as "boarders," and elderly patients with residual hemiplegias who were awaiting transfer to a hospital for chronic care. There was no significant difference in either the range or the mean value of hexosamine in these two groups.

The laboratory data were obtained from the hospital records, except for the hexosamine values. These were obtained by a modified Elson and Morgan method developed by one of the authors.¹³ All determinations were performed in duplicate, and the difference between duplicate runs was 2 per cent or less. Recovery experiments were frequently performed on samples of blood from normal persons and rheumatic fever patients and the added glucosamine was found to be quantitatively determined.

The erythrocyte sedimentation rate was determined on the adult service, by the method of Wintrobe and Landsberg, in Cases F.D., C.D., J.G., S.H., R.J., J.K., A.K., M.M., M.R., and S.S. On the pediatric service the Cutler method was used in Cases J.C., A.D., L.D., R.H., J.K., R.K., T.M., E.P., C.S., G.S., and A.Z.

PRESENTATION OF DATA

The plasma hexosamine level in seventy-six normal individuals ranged from 77 to 113 mg. per cent, lying between 80 and 105 mg. per cent in 92 per cent of this group. The mean value was 92 mg. per cent. Twenty-one patients with active rheumatic fever were studied. Their hexosamine levels together with their sedimentation rates are shown in Fig. 1. The onset of illness was arbitrarily established as that date upon which the patient first noted fever, malaise, joint pain, chest pain, or any of the signs and symptoms of rheumatic fever. The onset was not the day of admission as the patients frequently remained at home for several days or even weeks before coming to the hospital. For this reason, hexosamine levels at the very onset of the attack were rarely determined.

The pattern in active rheumatic fever was quite similar in many of the cases studied and was characterized by an elevation during the onset of the attack and then a return, sometimes very abrupt, to normal levels. This is shown in Fig. 2, which was derived by grouping of all the hexosamine determinations obtained in the twenty-one cases of active rheumatic fever into successive ten-day periods starting with the onset of the disease. The average value was then calculated for each of these ten-day periods and this level was plotted against the midpoint of each of these ten-day periods.

When the plasma hexosamine levels were correlated with the clinical course it was observed that patients with severe attacks of rheumatic fever, as judged by the height and duration of the fever and the intensity of the arthritis or carditis, demonstrated higher hexosamine elevations than those with mild episodes. It was also noted that manifestations of arthritis or carditis sometimes persisted after the hexosamine level had returned to normal. One such case is presented in detail in Fig. 3. On the forty-fifth day of illness the hexosamine level was at the upper limits of normal and remained so although for an additional forty-five days low-grade fever persisted and joint pains recurred whenever salicylates were stopped.

When the convalescent period was complicated by a second episode of rheumatic fever, there was a rise in the plasma hexosamine. Case A. D. (Fig. 1) was admitted with rheumatic polyarthritis and on the fifty-third day, during convalescence, the onset of chorea was noted. This was not accompanied by a change in

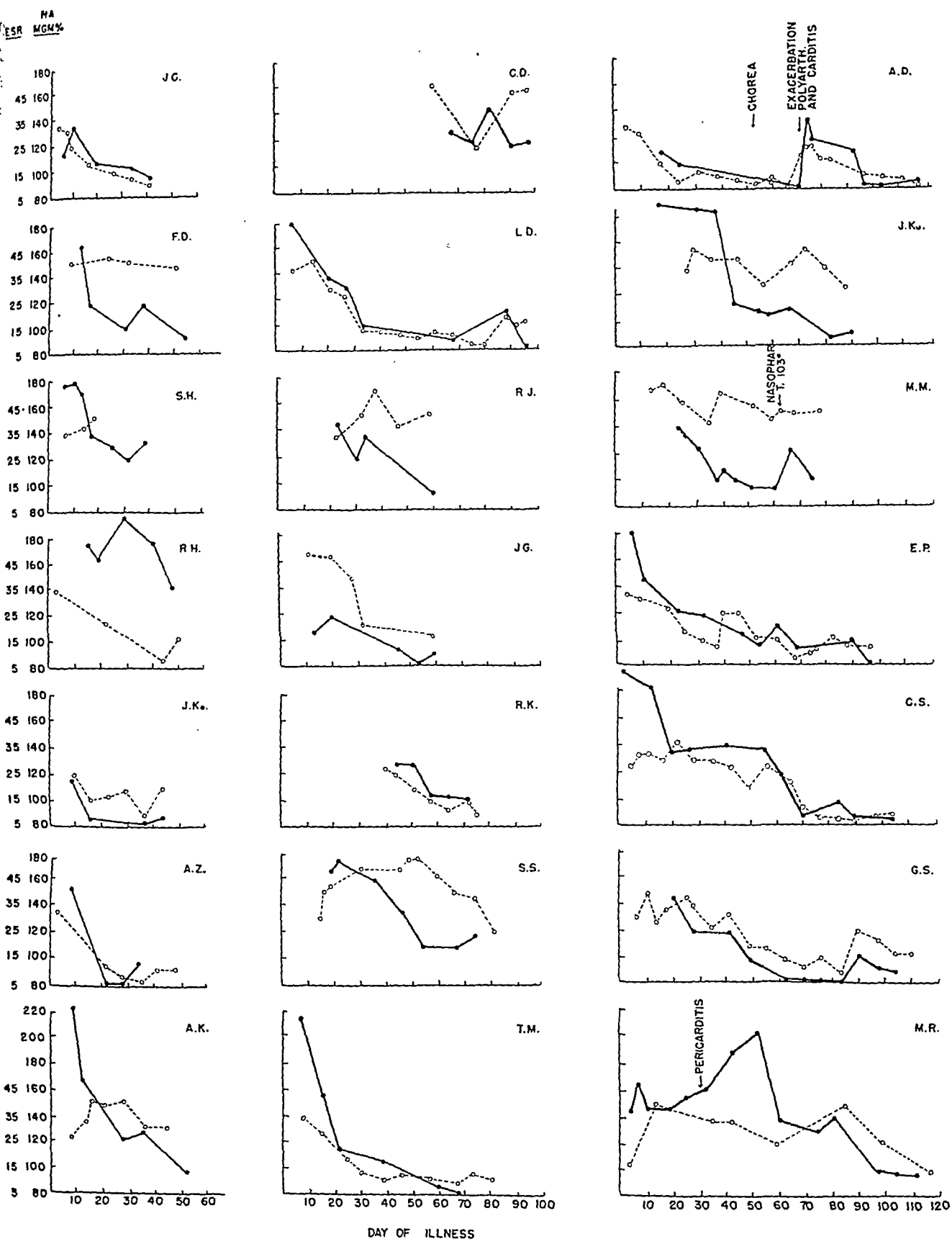


Fig. 1.—Plasma hexosamine levels (solid line) and erythrocyte sedimentation rates (broken line) in twenty-one cases of active rheumatic fever.

the hexosamine level. On the seventieth day, the patient manifested signs and symptoms of carditis and a renewal of the polyarthrititis. On this day the hexosamine level was 80 mg. per cent. Two days later, it was 106 mg. per cent, and two days after that it had risen to 130 mg. per cent. Another patient, demonstrating an additional rise in hexosamine accompanying an exacerbation of rheumatic fever, is Case M.R. presented in Fig. 4. In this patient, with an onset of pericarditis, the already elevated hexosamine rose to still higher levels.

The erythrocyte sedimentation rate and the plasma hexosamine parallel each other during most of the period of illness in ten of the twenty-one patients studied (Cases J.C., A.Z., L.D., R.K., T.M., A.D., E.P., C.S., G.S., and M.R.). In the remaining eleven patients there is either a negative or no apparent correlation or the data are too inadequate or too inconclusive to warrant any comparison.

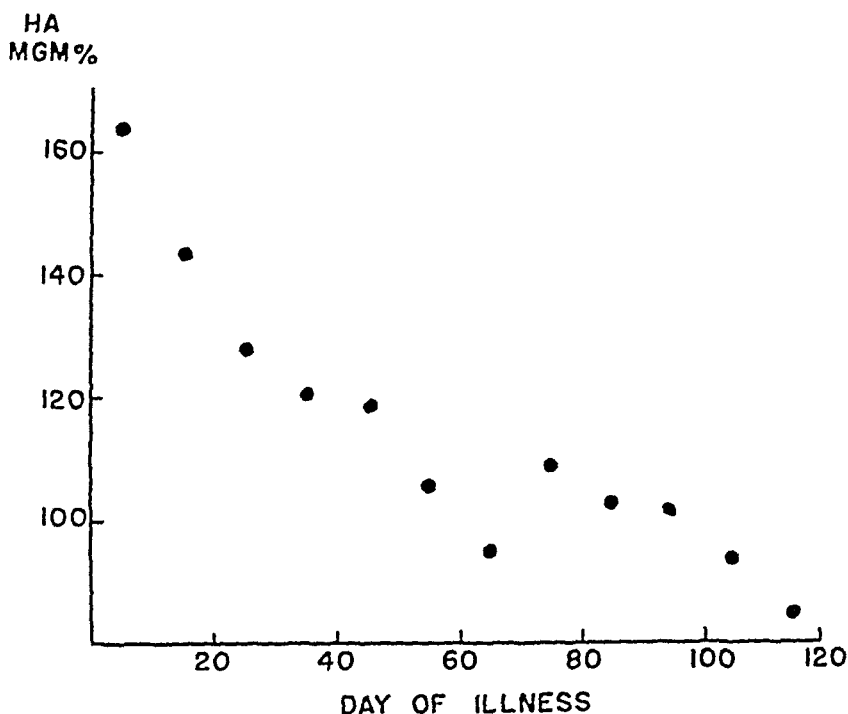


Fig. 2.—The points represent the average of all the plasma hexosamine levels in the twenty-one cases of active rheumatic fever after these levels had been grouped into successive ten-day periods starting with the onset of the illness.

Case M.M. (Fig. 1) developed a nasopharyngitis during the convalescent period and demonstrated a rise in the hexosamine with no evidence of renewed rheumatic activity. As had been mentioned, elevations in plasma hexosamine are not specific for rheumatic fever.

In addition to the twenty-one patients presented in Fig. 1, three patients with chorea alone and two patients with the end stage of rheumatic heart disease who died in congestive failure without clinical evidence of rheumatic activity (no post-mortem examination) demonstrated no elevation in their plasma hexosamine level.

Similar to the observations of West and Clarke,⁶ the plasma hexosamine was found to be elevated in a wide variety of illnesses (Table I). High levels were observed in acute pyelonephritis, pneumonia, gonococcal arthritis, subacute bacterial endocarditis, pulmonary tuberculosis, rheumatoid arthritis, multiple myeloma, and myocardial infarction.

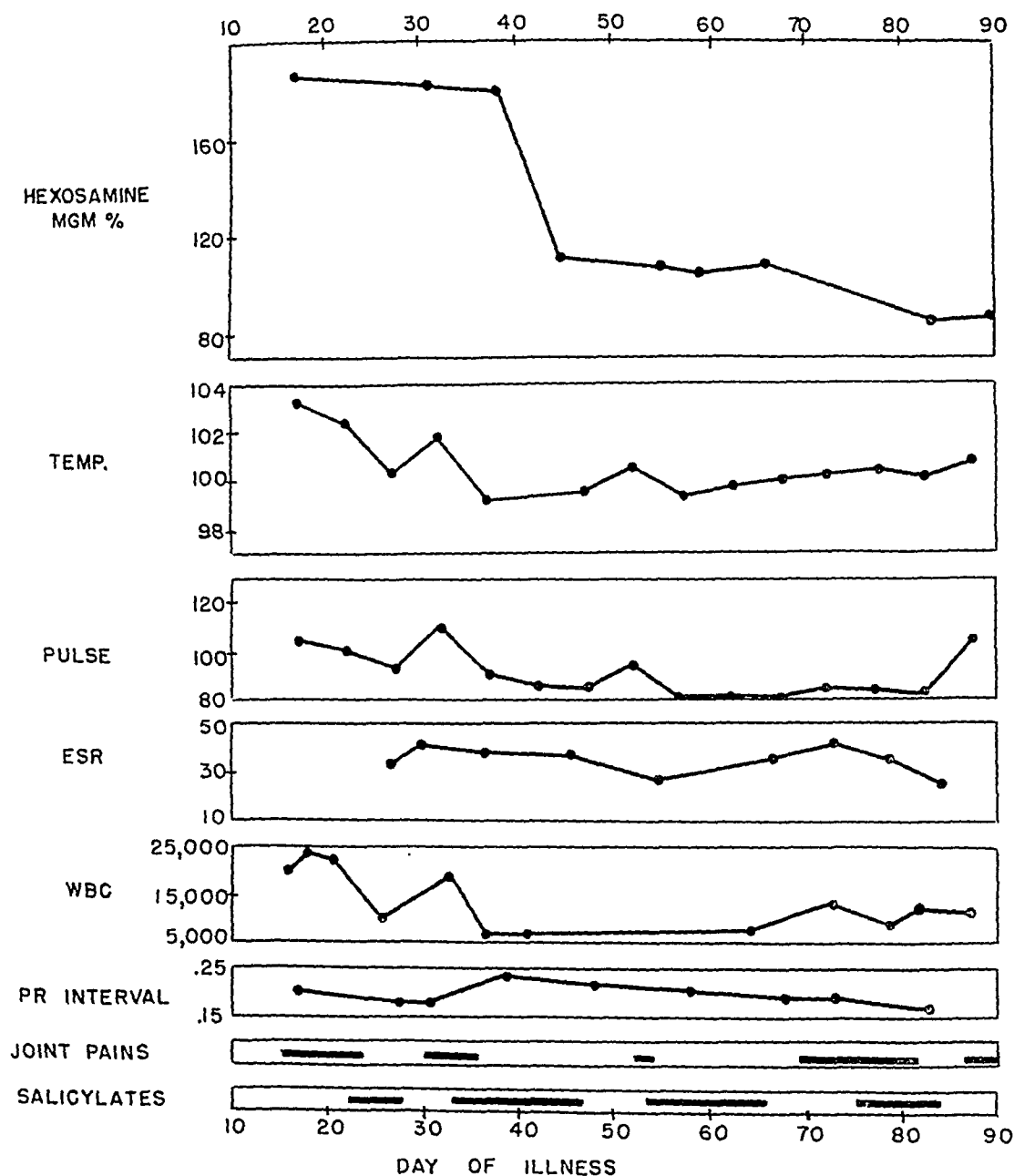


Fig. 3.—A 68-year-old man (J. K.) with a past history of rheumatic fever who was admitted to the hospital with fever and pain in right shoulder and right hip.

DISCUSSION

It is apparent, then, that in a multitude of diseases there is an elevation in the plasma hexosamine and presumably in the plasma polysaccharide. Regardless of the diversity of the offending agent, be it bacteria, sterile infarction, or malignancy, a similarity of response is evoked, namely, a rise in this substance. Its presence in the blood in increased amounts in such a wide variety of diseases suggests that part of the fundamental histochemical response of the body to

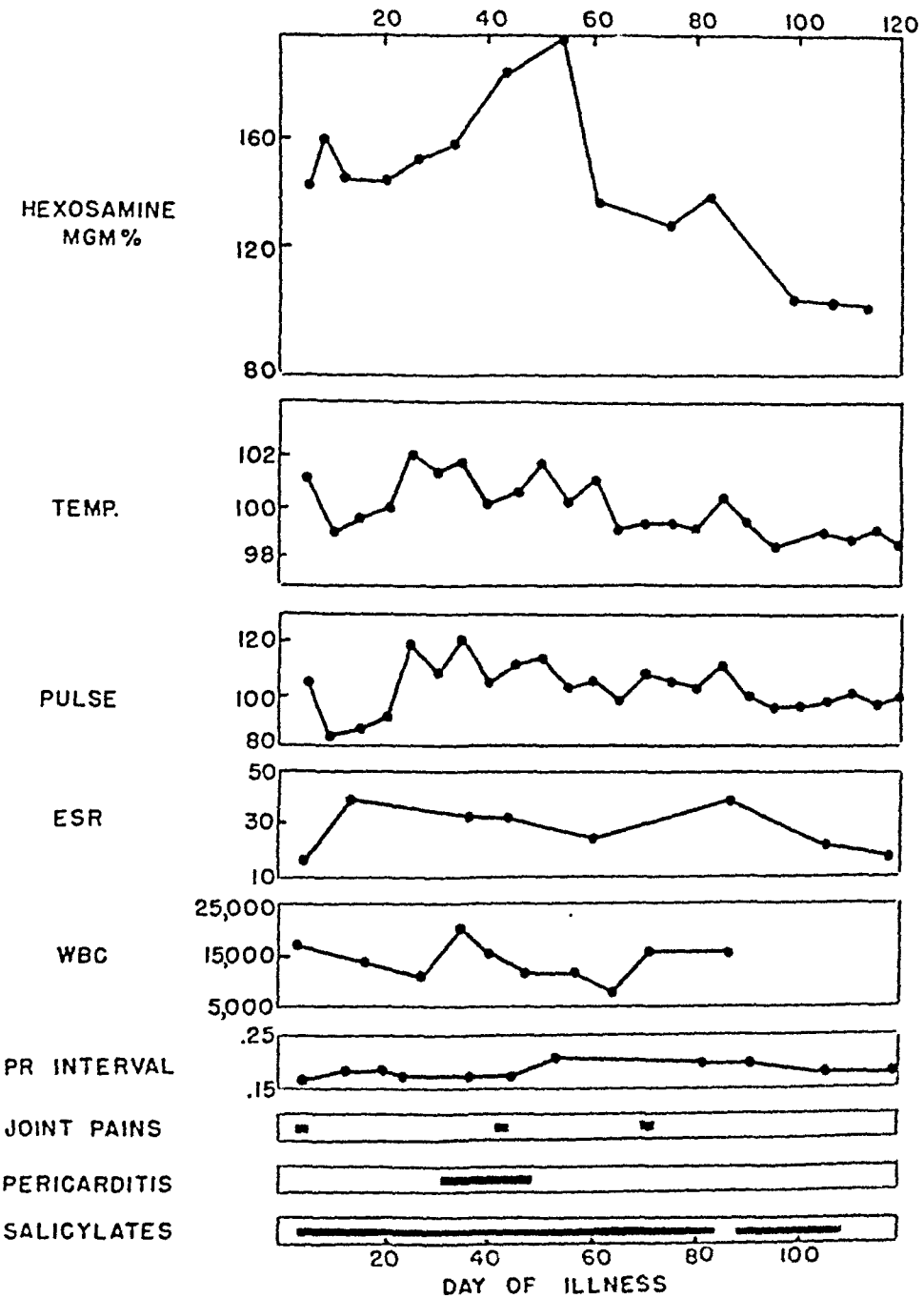


Fig. 4.—A 13-year-old boy (M. R.) with a past history of rheumatic fever and known rheumatic heart disease who was admitted to the hospital with fever and polyarthritits and subsequently manifested a pericarditis with marked effusion.

TABLE I. PLASMA HEXOSAMINE LEVELS IN DIFFERENT ILLNESSES

ILLNESS	HEXOSAMINE (MG. PER CENT)
Acute pyelonephritis	141, 165, 176, 124
Pneumonia	143, 144, 140
Pneumonia	138, 212
Pneumonia	122, 112, 107
Gonococcal arthritis	174
Gonococcal arthritis	134, 156, 142, 126
Gonococcal arthritis	107, 143, 145, 143
Subacute bacterial endocarditis	126, 141, 100, 77, 90
Pulmonary tuberculosis	130
Pulmonary tuberculosis	149
Pulmonary tuberculosis	170
Pulmonary tuberculosis	163
Rheumatoid arthritis	117
Rheumatoid arthritis	167
Multiple myeloma	148, 170
Myocardial infarction	70, 116, 122, 123, 97, 117, 116, 92

Each diagnosis represents an individual patient. The values opposite the diagnosis represent samplings taken during the illness in chronological order from left to right.

injury may be intimately connected with polysaccharide metabolism. It is known that polysaccharides are an important constituent of connective tissue. This, together with the frequency with which alterations in connective tissue occur in disease, suggests that the increased polysaccharide in plasma may be a reflection of the connective tissue response to disease. The data obtained from the twenty-one cases of rheumatic fever studied show that the highest polysaccharide levels were obtained during the early days of the more severe attacks. It may be that the degree and duration of polysaccharide increase is related to the mass of tissue involved in the rheumatic episode and the intensity of its involvement.

SUMMARY

Plasma hexosamine levels were followed in twenty-one patients with acute rheumatic fever, three patients with chorea, and two without clinical evidence of rheumatic activity who died in congestive failure with long-standing rheumatic heart disease. The plasma hexosamine was observed to be elevated in all twenty-one cases of acute rheumatic fever. The usual pattern was an elevation during the early portion of the episode and then a return to normal, which in several cases was very abrupt. The degree of elevation was greater in the severe cases than in the mild ones. In the three patients with chorea and in the two who died in congestive failure without clinical evidence of rheumatic activity, the hexosamine levels were normal. The erythrocyte sedimentation rate and the plasma hexosamine level roughly paralleled each other in ten of the twenty-one cases studied. In confirmation of the work of others, the plasma hexosamine elevation was not found to be specific for rheumatic fever and was observed to be increased in subacute bacterial endocarditis, pulmonary tuberculosis, pneumococcal pneu-

monia, acute pyelonephritis, gonococcal arthritis, rheumatoid arthritis, multiple myeloma, and myocardial infarction.

It is suggested that the increased plasma polysaccharide seen in this variety of diseases reflects a fundamental histochemical response to injury.

The authors wish to express their appreciation to Dr. Maxwell Schubert for his valuable comments and to Julia Morrison Einbinder for her technical assistance.

REFERENCES

1. Rimington, C.: (a) The Carbohydrate Complex of the Serum Proteins, *Biochem. J.* 25:1062, 1931.
(b) Seromucoid and the Bound Carbohydrate of the Serum Proteins, *Biochem. J.* 34:931, 1940.
2. Bierry, H.: Sur la nature du sucre protéidique dans le plasma sanguin du cheval, *Compt. rend. Soc. de biol.* 99:1837, 1928.
3. Hewitt, L. F.: The Polysaccharide Content and Reducing Power of Proteins and of Their Digest Products, *Biochem. J.* 32:1554, 1938.
4. Tillmans, J., and Philippi, K.: Ueber den gehalt der wichtigsten Proteine der Nahrungsmittel an Kohlehydrat und über ein kolorimetrisches Verfahren zur quantitative Bestimmung von stickstofffreiem Zucker in Eiweiss, *Biochem. Ztschr.* 215:36, 1929.
5. Elson, L. A., and Morgan, W. T. J.: A Colorimetric Method for the Determination of Glucosamine and Chondrosamine, *Biochem. J.* 27:1824, 1933.
6. West, R., and Clarke, D. H.: The Concentration of Glucosamine in Normal and Pathological Sera, *J. Clin. Investigation* 17:173, 1938.
7. Rosenow, E. C.: Studies in Pneumonia and Pneumococcus Infection, *J. Infect. Dis.* 1:280, 1904.
8. Longcope, W. T.: A Note Upon the Growth of Pneumococci and Streptococci in Blood Serum, *J. Exper. Med.* 7:626, 1905.
9. Friedemann, T. E., and Sutliff, W. D.: Appearance of Fermentable Polysaccharide in the Blood and a Simple Method for Its Detection, *Science* 90:335, 1939.
10. Youngner, J. S.: Relation of Sedimentation Rate to Amount of Precipitate Formed in Plasma by Type III Pneumococcus, *Proc. Soc. Exper. Biol. & Med.* 56:18, 1944.
11. Seibert, F. B., Nelson, J. W., and Seibert, M. V.: Correlation of Extent of Tuberculosis With Amount of Polysaccharide in the Serum, *Proc. Soc. Exper. Biol. & Med.* 52:219, 1943.
12. Seibert, F. B., Seibert, M. V., Atno, A. J., and Campbell, H. W.: Variation in Protein and Polysaccharide Content of Sera in the Chronic Diseases, Tuberculosis, Sarcoidosis, and Carcinoma, *J. Clin. Investigation* 26:90, 1947.
13. Schloss, B.: Unpublished data.

AN IMPROVED METHOD FOR VISUALIZING THE CORONARY ARTERIES AT POST MORTEM

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FROM the virtual inception of the study of anatomy, investigators have attempted to further their knowledge of the coronary circulation. As pointed out by Schlesinger,¹ the methods used fall into several categories as follows: (1) careful anatomical dissection; (2) injection of the coronary arteries with various substances such as agar and gelatin, and subsequent clearing of the heart muscle; (3) injection of the coronary arteries with material such as lead, and subsequent digestion of the heart muscle so as to leave a cast of the coronary artery bed; and (4) injection of the coronary arteries with radiopaque material and their study by roentgenograms to demonstrate the arterial tree.

An analysis of these techniques reveals the following disadvantages: (1) Information gained by gross dissection of the coronary arteries obviously is limited to macroscopic vessels and throws no light on the terminal ramifications of the coronary bed. (2) Methods of injection and subsequent clearing of the heart muscle by digestion preclude the histologic study of the myocardium as well as careful observations of the valve leaflets, orifices, and endocardium. (3) Roentgenographic studies prior to the work of Schlesinger were in general unsatisfactory because of the necessity of interpreting the location of the multiple small radicals thus demonstrated and also because of the confusion attendant on interpreting a three-dimensional specimen from a two-dimensional roentgenogram.

Gross² in 1921 published a method of visualizing the coronary bed which, although superior to previous methods, still had several disadvantages in that (1) it was a difficult technical procedure requiring complicated apparatus and (2) a period of twenty-four to forty-eight hours had to elapse before the specimen was ready for study.

Schlesinger and his co-workers² in 1936 developed a method for visualizing the coronary circulation which was distinctly superior to those previously used. The heart was so dissected that a roentgenogram of the specimen exhibited the coronary arterial circulation in one plane. Technically the method was simple and permitted a study of the circulation in a short time following the autopsy. However, the Schlesinger technique of dissection of the heart so distorts the

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architecture of the valves that they are unsatisfactory for study, and it is here that the pathologist not interested primarily in the minute coronary circulation objects to the trisection of the aortic and pulmonic valves. To meet these objections we have modified the Schlesinger technique of unrolling the heart so as to preserve the valves intact and without distortion.

The initial incision is made through the left cusp of the pulmonic valve and carries down along the entire right border of the interventricular septum to the apex of the heart, opening up the right ventricular cavity (Fig. 1). The second incision is made through the anterior portion of the left coronary cusp of the



Fig. 1.—Incision made through the left leaflet of the pulmonic valve and extended along the entire right border of the Interventricular septum to the cardiac apex.

aortic valve (thus preserving the valve commissure between the right and left coronary cusps) and is extended into the cavity of the left ventricle, care being taken to avoid the main left coronary trunk. This incision is then extended to join the cut surface of the right ventricle and is carried down to the cardiac apex freeing the anterior margin of the septum (Fig. 2). The previously isolated main coronary trunks are now severed from the aorta immediately distal to their ostia with a sharp scalpel and the auricles are widely opened by incisions joining the superior and inferior venae cavae and the pulmonary veins, respectively

A finger can now be readily passed from the left auricle into the left ventricle and dissection scissors guided upward through the lateral margin of the mitral valve orifice and thence between the wall of the aorta and the severed end of the left coronary artery and extending through the auricular musculature. Thus, the entire left side of the specimen is opened. It will be readily unrolled into a single plane after section of two or three chordae tendineae extending to the mitral valve from the posterior papillary muscle. The pulmonary artery segment is now freed from the aortic valve ring by blunt dissection along the planes of cleavage and a similar incision is made on the right side of the interventricular septum (care being taken first to pass an examining finger through the tricuspid

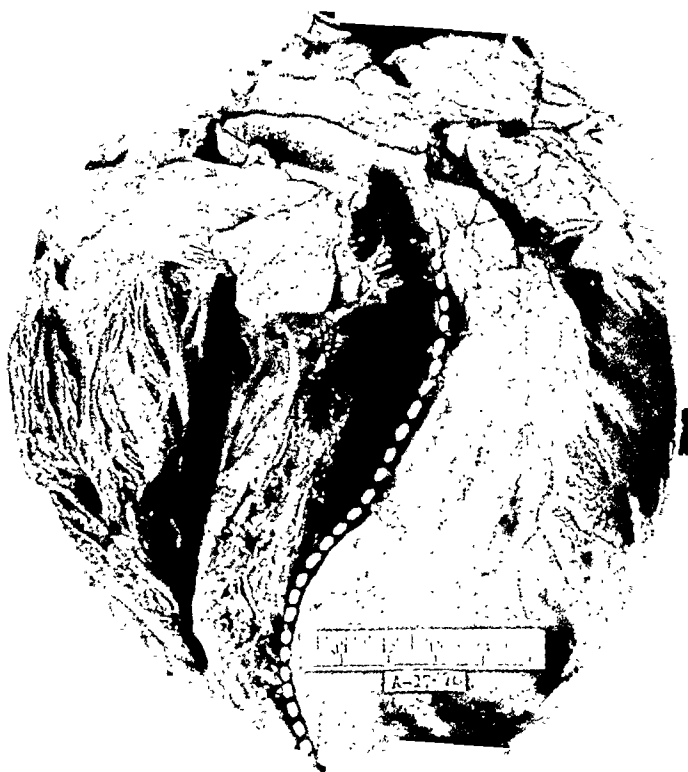


Fig. 2.—Second incision completed through the anterior portion of the left coronary cusp of the aortic valve into the cavity of the left ventricle and then extended to join the cut surface of the right ventricle and down to the cardiac apex.

orifice to facilitate passage of the dissecting scissors upward through the tricuspid valve between the aortic wall and pulmonary artery and avoiding the cut end of the right main coronary trunk), an incision which will enable the right side of the entire specimen to be unrolled for examination (Fig. 3). The final incision consists merely of removal of the interventricular septum in its entirety by dissection through the undefended space and along the posterior border of the septum from base to apex, to connect with the first incision, thus permitting ready removal of the entire septum, which may be placed beneath the main specimen when roentgenograms are made as described by Schlesinger (Fig. 4).

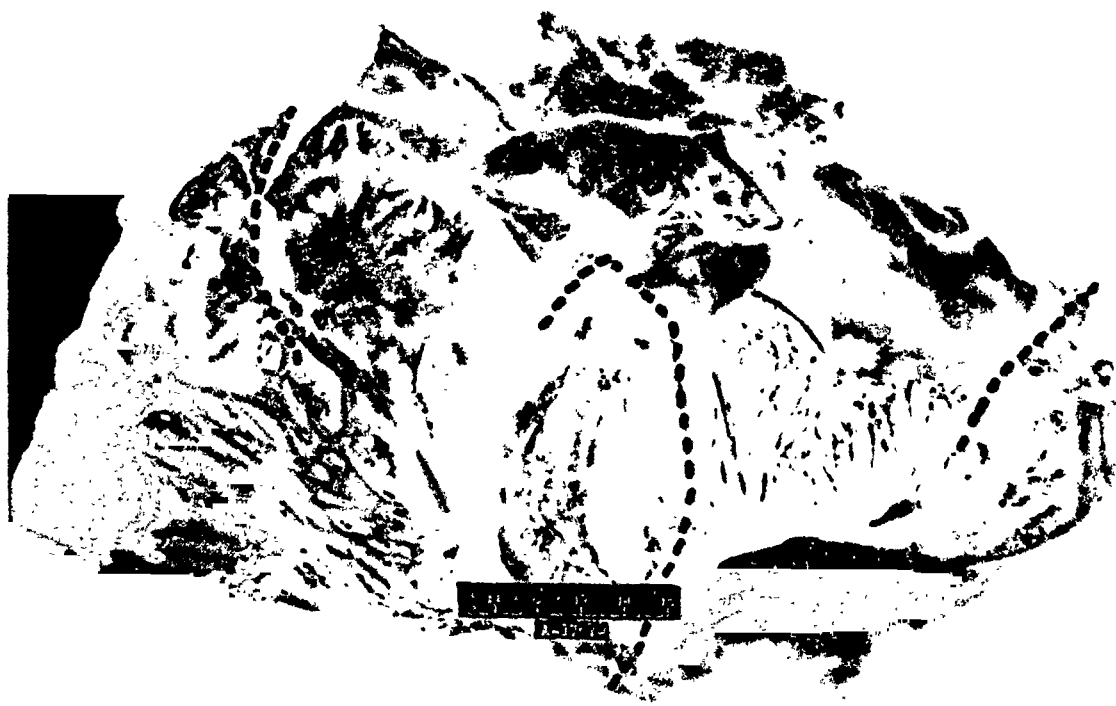


Fig. 3.—Specimen after incisions through the lateral margin of mitral valve and tricuspid valves and extending through the auricular musculature have been completed (lines of incision indicated by dotted lines). The central line represents path of final dissection for removal of the interventricular septum.

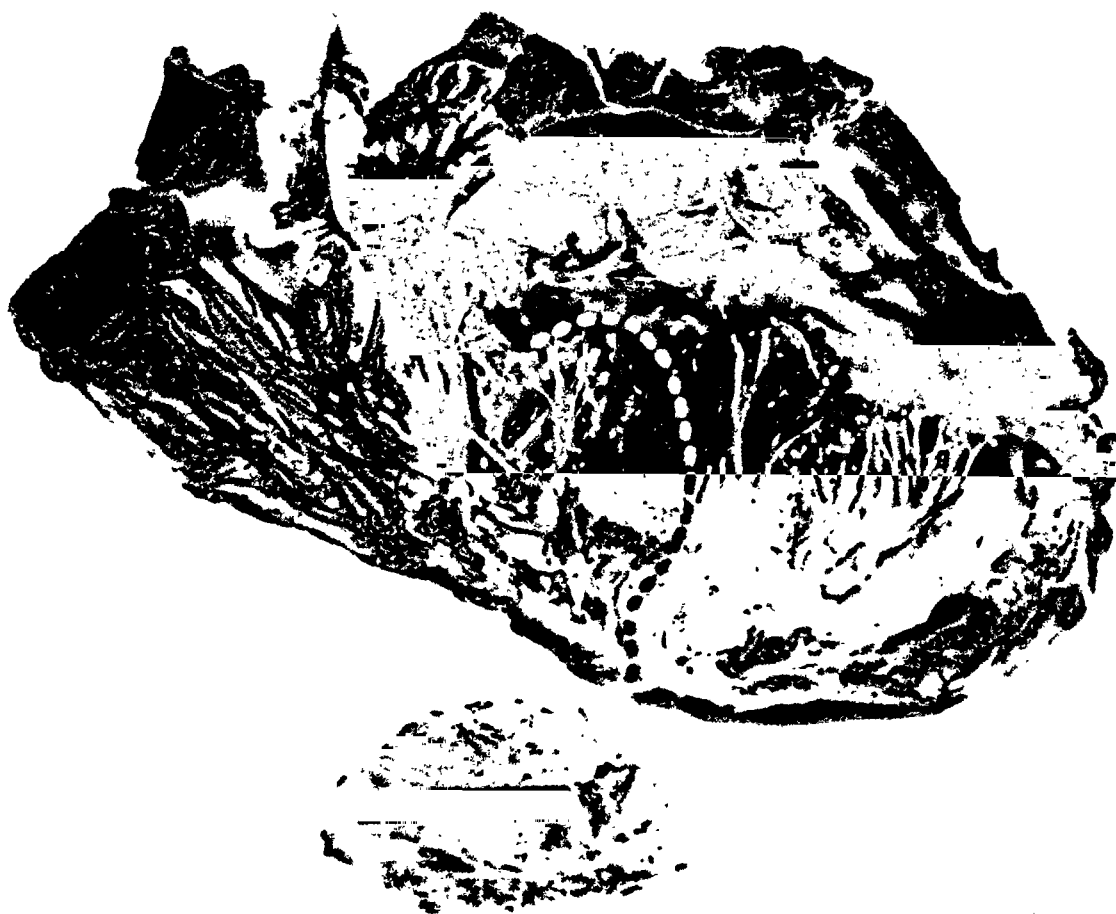


Fig. 4.—Specimen after dissection is completed. The interventricular septum has been removed by dissection through the undefended space and extending along the posterior border of the septum from base of apex.



Fig. 5.—Roentgenogram of normal heart after completion of injection. The anastomotic communications and terminal ramifications of the two main coronary arteries are demonstrated.



Fig. 4. Roentgenogram of a specimen showing extensive coronary arteriosclerosis. The main right coronary artery from C to A was the seat of a fresh thrombus. Both the posterior descending ramus and the terminal right main coronary artery to the left of A were filled with red mass injected into the left coronary artery. At B was an old occlusion partially recanalized. The area within the dotted line was the seat of fresh infarction.

Salans and Tweed⁴ in a preliminary report introduced the use of liquid latex and barium sulfate as the injection mass in an effort to improve the technique described by Schlesinger. This technique, however, necessitated alcohol fixation of the myocardium and subsequent refrigeration which, while time consuming, did not in any way distort the histologic pattern and, in fact, facilitated microscopic examination because the various colors of the injection mass were retained in the histologic preparations.

We have modified the technique of Salans and Tweed as follows: Using their injection apparatus, we have found it unnecessary to suspend the specimen in glacial acetic acid and alcohol as they did; the heart may lie in a flat-bottomed jar during the injection. After the injection it is not necessary to place the specimen in glacial acetic acid and alcohol to harden the injection mass since one may accomplish this by placing the specimen in the standard deep-freeze unit for one and one-half to two hours, after which roentgenograms, as well as sections of the coronary arteries and the myocardium, may be made without any extravasation of the colored injection mass. The injection mass* employed has been that described by Salans and Tweed, except that the particle size of the injection mass has been standardized by screening, ocular micrometer examination, and viscosity determinations, so that the size of the individual particles is standard at 14 micra, a uniformity which permits examination down to and including vessels of this specified caliber but does not extend into the capillary or other small sinusoidal channels.

To facilitate injection we have adopted a method of inserting the glass cannulae into the coronary ostia and fastening them in place as follows: The right and left main coronary trunks are isolated by blunt dissection immediately distal to their respective ostia and a short length of regular upholsterer's thread is passed around the trunk. A glass cannula is then inserted into the coronary ostium. It is secured in place by passing both ends of the previously placed thread through a short length of glass tubing, the ends of which have been especially blunted, and subsequently pulling both sections of thread taut and keeping it so by a small hemostat. This technique of inserting the cannulae is easy and permits their ready removal after the injection is completed.

Roentgenograms† of specimens prepared by our technique are shown in Figs. 5 and 6. Fig. 5 shows a normal coronary bed, while Fig. 6 shows a specimen similarly prepared but one in which the coronary arteries show marked arteriosclerosis and several old occlusions.

*A suspension of barium sulfate in an aqueous ammoniated solution of liquid latex is used. Compound No. 60-22724A (red), No. 60-22724B (blue), and No. 60-24899 (white) were obtained from the American Anodé Company, Akron, Ohio.

†Two types of film were employed, both screen and nonscreen, in cardboard holders. The technique used with the nonscreen film was 0.3 second, 100 milliamperes, and 41 kilovolts at a 30-inch target-film distance. The technique used with the screen film was 1.0 second, 100 milliamperes, and 40 kilovolts at a 30-inch target-film distance.

SUMMARY

A technique for visualizing the coronary bed of the heart has been described which has certain advantages over previously described methods. It is simple and the entire procedure requires only two hours. The method of dissection preserves the cardiac valves, and the injection mass, which is color fast, does not distort the histologic picture of the myocardium.

The authors gratefully acknowledge the technical assistance of Miss Lucy Krayeris in the development and standardization of the x-ray technique used in this study.

REFERENCES

1. Schlesinger, M. J.: Blood, Heart, and Circulation Symposium, American Association for the Advancement of Science. Publication 13, Washington, D. C., 1940, The Science Press Printing Company, p. 61.
2. Schlesinger, M. J.: Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15:528, 1938.
3. Gross, L.: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber, Inc., p. 4-10.
4. Salans, A. H., and Tweed, Phyllis: A Preliminary Study of The Coronary Circulation Post Mortem, *AM. HEART J.* 33:477, 1947.

NECROSIS IN THE CORONARY ARTERIES OF NEWBORN INFANTS

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THE subject of the present report is a necrotic lesion in the coronary arteries of stillborn and newborn infants. In view of its frequent occurrence it appeared desirable to call attention to these findings even though their significance for the function of the heart and for the organism as a whole is not yet understood.

Twenty-one infants listed in Table I showed the lesion which will be described presently. Other pathologic findings in the same infants are also listed, in order that a correlation with the changes in the coronary arteries may be attempted. The considerable frequency of the arterial lesion is evident from Table II. In both tables a prominent place is given to data on the occurrence of those other changes which are commonly interpreted as signs of asphyxia. They include hemorrhages in the epicardium and other parts of the body, aspiration of large amounts of vernix caseosa into the lungs, and general venous congestion. These are the only findings which are nearly constant in the patients with arterial lesions; however, there are many more infants with these signs of asphyxia in which the coronary arteries are not affected. The possible mutual relations of these changes will be discussed. As is often the case in neonatal pathology, no constant and significant data could be obtained from the clinical history.

The majority of the autopsies among which changes in the coronary arteries were encountered were performed at Kings County Hospital. The balance of the material has been obtained through the cooperation of various hospitals in Brooklyn. Tissues were preserved in the usual manner in 10 per cent Formol, Bouin's solution, or Zenker's fixative. Heart sections of one to three paraffin blocks were routinely stained with hematoxylin and eosin. Whenever lesions in the coronary arteries were found or suspected, additional blocks, as well as special stains, were used, including Masson's or Mallory's trichrome stain, Weigert's method for elastic tissue, phosphotungstic acid hematoxylin, and Gömöri's silver impregnation of lattice fibers. Bacterial stains were used in some of the cases and uniformly failed to demonstrate microorganisms in the abnormal areas.

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Publication No. 3 of the Brooklyn Survey of Neonatal Pathology. Many hospitals in Brooklyn are contributing pathological material to this survey. The project is supported by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

6. The gratifying response of this small, though representative series of gravely ill patients would seem to indicate that heparin/Pitkin menstruum, because of its simplicity of administration, prompt effectiveness, and absence of toxicity, is well suited for the treatment of acute coronary artery thrombosis and its complications.

The authors are indebted to Miss M. D. VanWart and Miss F. Kashdan for their technical assistance.

REFERENCES

1. Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin: Preliminary Report, *Am. J. M. Sc.* **208**:54-63, 1944.
2. Loewe, L., Rosenblatt, P., and Hirsch, E.: Venous Thromboembolic Disease, *J. A. M. A.* **130**:386-393, 1946.
3. Loewe, L., and Hirsch, E.: Heparin in the Treatment of Thromboembolic Disease, *J. A. M. A.* **133**:1263-1268, 1947.
4. Richter, I. H., Eiber, H. B., and Loewe, L.: Subcutaneous Heparin in the Treatment of Arterial Thrombotic Disease: Preliminary Report, *Surgery*, **22**:489-495, 1947.
5. Greene, H. J., and Loewe, L.: Anticoagulation Therapy With Heparin/Pitkin Menstruum in Thromboembolic Disease Complicating the Puerperium and Gynecological Surgery, *Am. J. Obst. & Gynec.* **54**:958, 1947.
6. Bancroft, F. W.: Proximal Ligation and Thrombectomy for Phlebothrombosis of the Femoral and Iliac Veins, *Ann. Surg.* **121**:175, 1945.
7. Evans, J. A., and Boller, R. J.: The Subcutaneous Use of Heparin in Anticoagulation Therapy, *J. A. M. A.* **131**:879-882, 1946.
8. Bancroft, F. W.: The Surgical Treatment of Phlebothrombosis in Obstetrics and Gynecologic Patients, *Am. J. Obst. & Gynec.* **53**:109-116, 1947.
9. Loewe, L.: Anticoagulation Therapy With Heparin/Pitkin Menstruum in Thromboembolic Disease, *Am. J. Med.* **3**:447-467, 1947.
10. Blumer, G.: The Importance of Embolism as a Complication of Cardiac Infarction, *Ann. Int. Med.* **11**:499, 1937.
11. Loewe, L., Hirsch, E., and Grayzel, D. M.: The Action of Heparin on Experimental Venous Thrombosis, *Surgery* **22**:746-760, 1947.
12. Gradwohl, R. B. H.: *Clinical Laboratory Methods*, ed. 3, St. Louis, 1943, The C. V. Mosby Company, p. 514.
13. Macht, D. I.: Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs, *Ann. Int. Med.* **18**:772, 1943.
14. De Takats, G., Trump, R. A., and Gilbert, N. C.: Effect of Digitalis on Clotting Mechanism, *J. A. M. A.* **125**:840-845, 1944.
15. Solandt, D. Y., and Best, C. H.: Heparin and Coronary Thrombosis in Experimental Animals, *Lancet* **2**:130-132, 1938.
16. Nichol, E. S., and Page, S. W., Jr.: Dicumarol Therapy in Acute Coronary Thrombosis; Results in 50 Attacks, With Review of Data on Embolic Complications and Immediate Mortality in Myocardial Infarction, *J. Florida M. A.* **32**:365-370, 1946.
17. Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, *J. A. M. A.* **130**:398-403, 1946.
18. Wright, I. S.: Experiences With Dicumarol (3,3' Methylene-Bis 4-Hydroxycoumarin) in the Treatment of Coronary Artery Thrombosis With Myocardial Infarction: Preliminary Report, *AM. HEART J.* **32**:20-31, 1946.
19. Parker, R. L., and Barker, N. W.: The Use of Anticoagulants in the Management of Acute Myocardial Infarction: Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **22**:185-192, 1947.
20. Best, C. H.: Heparin and Thrombosis, The Harvey Lectures, 1940-1941, New York, Science Press Printing Company, p. 66.
21. Prandoni, A., and Wright, I.: The Anticoagulants; Heparin and the Dicoumarin-3,3' methylene-Bis-(4-hydroxycoumarin), *Bull. New York Acad. Med.* **18**:433-458, 1942.
22. Cahan, A.: Hemorrhage and Purpura Caused by Dicoumarin, *New England J. Med.* **228**:820, 1943.
23. Wasserman, L. R., and Stats, D.: Clinical Observations on the Effect of 3,3'-methylenebis (4-hydroxycoumarin), *Am. J. M. Sc.* **206**:466, 1943.
24. Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicumarol Therapy With Autopsy Findings, *Ann. Int. Med.* **21**:332, 1944.
25. De Takats, G., and Fowler, E. F.: The Problem of Thromboembolism, *Surgery* **17**:153, 1945.
26. Quick, A. J.: *The Hemorrhagic Diseases and the Physiology of Hemostasis*, Springfield, Ill., 1942, Charles C Thomas, Publisher, pp. 111, 112.

TABLE II. CORRELATION OF NECROSIS IN CORONARY ARTERIES WITH HEMORRHAGES IN THE EPICARDIUM, AND BODY LENGTH IN INFANTS UP TO THREE DAYS OF AGE, INCLUDING NONMACERATED STILLBORN INFANTS

	ALL INFANTS EXAMINED		CASES WITH NECROSIS IN CORONARY ARTERIES		
	NUMBER OF CASES	AVERAGE BODY LENGTH	NUMBER	PER CENT	AVERAGE BODY LENGTH
Hemorrhages in epicardium	98	45.3	18	18.4	49.9
No hemorrhages in epicardium	123	40.2	3	2.4	47.7
Total	221		21	9.5	

The essential features of the abnormality are best described by referring to typical lesions, as illustrated in Figures 1 to 8. The most conspicuous form of the lesion is exemplified by Case 13 (Fig. 1). At the border of the media and the adventitia of many arteries there are masses of eosinophilic material enclosing cavities filled with debris and an occasional erythrocyte. In some instances these areas are small, and in others they surround most or all of the vessel. The abnormal material extends toward the lumen of the artery to a varying extent, replacing part of the media. In the present patient most of the lesions do not penetrate the entire thickness of the media, and the intima is intact everywhere. The affected arteries are dilated, and the internal elastic membrane shows little or none of the scalloping which would indicate a contraction of the media. The tissue surrounding these arteries shows greatly dilated veins and capillaries, as well as extravasation of blood from the vessels, as it is commonly seen in the epicardium of asphyxiated newborn infants. There is moderate increase in the number of various white blood cells distributed in the tissue spaces of the epicardium. The lungs in this infant showed interstitial emphysema, with collections of air in the septa and under the pleura. Some of these spaces were partly filled with turbid fluid, and about 10 c.c. of similar fluid was contained in each pleural cavity. Bacterial cultures and stains were negative.

Case 10 shows the typical hemorrhages in pleura and epicardium which are often associated with asphyxia (Fig. 2). In the arteries in the epicardium there are again foci of eosinophilic material, in this patient replacing the entire media (Fig. 3); they do not contain the large vacuoles seen in Case 13. There are a few distorted nuclei in these areas. The intima is intact. Dilatation of all vessels and extravasation of blood are present as in the preceding patient, but there is no appreciable infiltration with white blood cells.

A greater variety of changes is found in the coronary arteries of Case 16, both in the epicardium and in the myocardium. In addition to areas resembling that shown in Fig. 3, there are others in which the media is transformed into a group of spaces filled with finely granular material (Fig. 4) which is more uniform in appearance than the debris shown in Fig. 1. In large areas the media is entirely destroyed, and extravasated blood is seen surrounding the intact intima (Fig. 4). The same patient shows a peculiarity which is not typically associated with the

electrocardiographically because of the displacement of the transitional zone into the axilla. The low voltage of the initial R wave in Leads V_4 and aV_L might have been secondary to infarction of the free wall of the left ventricle, but diagnostic signs of this lesion were absent. An old patchy infarct of the basal portion of the anterior wall (represented by the broken lines in Fig. 5) was also obscured by the right bundle branch block. A separate patchy infarct of the posterior wall, also indicated by broken lines, was not evident electrocardiographically, probably because of transmission of the potential variations of the right ventricle to the left leg.

CASE 74.—A 62-year-old man had had angina pectoris for three years. Attacks were brief in duration until ten days before hospital admission, when he was seized with severe retrosternal pain which lasted three days. He arose from bed for the first time on the day of admission and collapsed on the street with a recurrence of retrosternal constriction and dyspnea. He was brought to the hospital in shock and died five days later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 3, *E*. Attention is directed to the similarity of this tracing to that obtained on December 1 in Case 69 (Fig. 1). The initial Q and tall R waves of Lead V_1 , together with the delay in onset of the intrinsicoid deflection to 0.10 second, were indicative of right bundle branch block due to infarction of the interventricular septum. The slight elevation of the RS-T segment in Lead V_1 suggested that the septal lesion was of recent origin. Because of the broad S wave in all leads to the left of Lead V_1 , it was concluded that the transitional zone was near the left sternal border and that Leads V_2 through V_6 reflected the potential variations of the anterolateral wall of the left ventricle. The abnormal Q wave and the upward displacement of the RS-T junction in Leads V_2 through V_6 were construed as evidence of continuation of the recent septal infarct into the anteroseptal and anterolateral aspects of the left apex. The small R and broad S waves of Lead aV_L represented the pattern recorded over the normal left ventricle in right bundle branch block and were probably transmitted from an uninfarcted basal portion of the lateral wall. From a first glance at Leads aV_F , II, and III, one might be tempted to attribute the abnormal Q wave in these leads to coexistent posterior infarction. However, the late intrinsicoid deflection in Lead aV_F indicated that this lead, like Lead V_1 , reflected the potential variations of the right ventricle. Thus, the abnormal Q wave in Leads aV_F , II, and III, like that in Lead V_1 , could have been produced by the septal infarction.

Pathologic Findings.—The heart weighed 430 grams and exhibited a recent infarct of the interventricular septum which extended into the anterolateral and posteroapical aspects of the left ventricle in a manner almost identical with that in Case 69 (Fig. 2). The right ventricle was uninvolved. The infarct of the anterior wall of the left ventricle was confined to the subendocardial one-half except in the apical segment, where it was transmural, and thus was well correlated with the findings in Leads V_2 through V_6 . The entire interventricular septum was infarcted, not only in the first four segments, as in Fig. 2, but also in the basal segment, as well. This accounted for the abnormal QRS-T pattern in Leads V_1 and V_2 . In addition to the extension of the acute infarct into the posterior aspect of the apical segment, there was an old, completely healed, patchy infarct occupying the basal three-fifths of the posterior wall of the left ventricle. Nevertheless, the abnormal Q wave recorded in Leads aV_F , II, and III was believed referable to the infarction of the septum rather than to the lesion of the posterior wall, for reasons already given.

CASE 75.—A 58-year-old man gave a typical history of angina pectoris, beginning two months before hospital admission, and was hospitalized in his first prolonged attack of retrosternal constriction. Despite strict confinement to bed, there were repeated attacks of retrosternal pain, usually relieved by nitrites and papaverine. Systolic and diastolic pressures were consistently subnormal. The patient suddenly died during a meal on the thirty-third day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the twelfth hospital day is reproduced in Fig. 6, *A*. Right bundle branch block was established by the tall, coarsely slurred R wave and the 0.10 second interval preceding the intrinsicoid deflection in Lead V_1 . A diagnosis of infarction of the septum was made from the presence of a Q wave instead of the expected initial

Another example of transformation of the media into a necrotic mass with cavities filled with granular debris is Case 21 (Fig. 6). In this patient there are also arteries in which the media has disappeared, and a moderate aneurysmal dilatation has occurred. This dilatation seldom exceeds in width the space vacated by the disappearance of the media, and an intact internal elastic layer can be demonstrated throughout the lesion (Fig. 7). In other instances, such as that shown in Fig. 8 (Case 3), the media disappears without leaving a trace, and without the development of bulging of the weakened vessel walls.

The lesions in all other cases listed in Table I conform to the descriptions just given. The occurrence of the various forms of necrosis in each patient will not be described in detail.



Fig. 4.—An artery in the myocardium of Case 16. The media is preserved only in the lowermost portion of the figure. The remainder of the media is either destroyed and replaced by hemorrhage, or transformed into cavities filled with finely granular material (at arrow). (X350)

Fig. 5.—An artery in the epicardium of the same patient shows a small thrombus in the lumen, attached to a portion of the wall in which the intima cannot be seen, and the media is replaced by eosinophilic material. (X250)

Search of the literature has revealed only one report possibly related to the changes under consideration.¹ This was the case of a 3-day-old infant in which the intima and adjacent portion of the media of the coronary arteries was intact, whereas the outer portion of the wall stained poorly and had an "almost hyaline-like"¹ appearance. The published description and figures do not permit a decision as to whether or not this is an instance of the same pathological condition as that described here. One wonders why these conspicuous lesions have not received more attention in the past. This is probably not due to oversight on the

ing eighty-nine cases. These cases were classified into three groups, according to the distribution of the lesion at autopsy: Group A, infarction primarily in and largely confined to the septum in six cases; Group B, septal extension of large anterior or anteroposterior infarction in fifty-nine cases; Group C, septal extension of posterior infarction in twenty-four cases.

The following electrocardiographic patterns could be correlated directly with the septal infarct found at autopsy:

1. Complete A-V block was observed as a manifestation of extension of an acute posterior infarct into the base of the septum in two cases.

2. A QRS interval of 0.12 second or more, a prominent late R wave, and a delayed intrinsicoid deflection in leads from the right precordium were found in fourteen cases and were attributable to septal infarction in thirteen of the group because of the presence of a distinct Q wave and/or abnormally elevated RS-T junction in these leads. The infarct was confined to the apical one-half to two-thirds of the septum in five of the cases and probably caused delay in right ventricular activation by interruption of conduction through the right Purkinje system, rather than the right bundle branch. Since the electrocardiographic findings in these cases were similar to those in other cases with infarction reaching the anatomic site of the bundle of His, the customary term, "right bundle branch block," was retained to designate the conduction defect. The abnormal Q wave in right ventricular leads constituted the chief distinguishing feature from uncomplicated right bundle branch block and was recorded because of the preponderance of negative potentials transmitted from the left ventricular cavity through the infarcted septum to the right precordium over reduced positive potentials coming from activation of intact remnants of septum. The differentiation of infarcts limited to the septum from those continuing into the anterior wall of the left ventricle depended upon the QRS pattern in leads to the left of the transitional zone and was rendered difficult in three of the cases of right bundle branch block by displacement of the transitional zone into the left axilla. The recognition of extension of a septal infarct into the posterior wall of the left ventricle was possible from Lead aV_R in intermediate to vertical cardiac position, but not in transversely placed hearts, since reference of the potential variations of the right side of the septum to the left leg, as a result of horizontal position, produced patterns in Leads aV_R , II, and III which simulated those caused by posterior infarction. The standard limb leads did not reveal diagnostic evidence of septal infarction in any of the thirteen cases.

3. A QRS interval of 0.12 second or more, an initial upstroke in all leads facing the left ventricle, and an abnormally delayed intrinsicoid deflection in left axillary leads were found in four cases and were attributed to left bundle branch block independent of the septal infarct in three of these. In the remaining case, autopsy revealed an acute infarct limited to the left side of the apical two-thirds of the septum and the subendocardial layer of the anterior and posterior walls of the left ventricle, and the pattern was attributed to septal activation by impulses distributed through the right Purkinje plexus.

4. Patterns characterized by a QRS interval of 0.12 second or more, an initial Q wave, and a late intrinsicoid deflection in precordial leads over the left

fixatives. In the majority of the cases the preservation of the tissues is generally good, and changes similar to those in the heart were found only in the liver, as will be mentioned subsequently. All these factors indicate that one is not dealing with artifacts. Relying on these facts, as well as on the observation of various stages of the lesion and their demonstration with a variety of staining methods, the conclusion that the changes occurred during life has been reached.

The following common features are present in the great majority of all foci of necrosis. The outer portion of the media is affected, and tissue damage may extend inward to a varying depth. The adventitia is the seat of edema and hemorrhage, and, in a few instances, also of a moderate leucocytic infiltration. The intima is usually intact, which accounts for the fact that thrombosis in the lumen is not the rule. The above-mentioned change in the adventitia is not limited to those areas in which the media is visibly damaged. It is widely distributed along the vessels of the heart in these infants, as well as in others showing congestion and foci of hemorrhage, as these conditions are commonly believed to be associated with anoxia. This association will be discussed. At this point it should be emphasized that necrosis of the media occurs in some of those areas in which edema and hemorrhage have affected the adventitia. This fact, together with the observation that the lesion appears to progress from the adventitia toward the intima, suggests that perhaps the nutrition of the vessel wall, derived from the adventitia, is defective in the areas of necrosis. A thin, inner layer of the vessel wall, comprising the intima and in some cases the adjacent part of the media, may be assumed to be preserved because it draws its supplies from the lumen of the artery.

It is difficult to judge the extent to which necrosis in the media of arteries, as described here, affects the function of these vessels. Extreme dilatation of the artery is not limited to the segments with visible damage to the media, but occurs throughout the heart of an asphyxiated newborn infant, regardless of the occurrence of necrosis. Electrocardiographic evidence suggests myocardial damage in asphyxiated newborn infants,² but there is no reason to believe that this depends on the changes described here. Thrombosis in arteries with necrosis is rare and never complete, and rupture of an artery has not been seen. It is possible, therefore, that arteries with necrosis do not differ functionally from others in the same organ. Whether recovery from anoxia is influenced by necrosis in the media is not known.

It will be noted that no late stages were observed in older infants, and this indicates either that all infants with these lesions die, or that the destroyed tissue regenerates rapidly. The former alternative could mean that the lesion in question is fatal, or that it is a terminal event. The possibility of rapid and complete regeneration must be seriously considered, since the regenerative power of the tissues may well be greater in the newborn than in the adult, who serves as the standard in human pathology. At this time, no decision can be made as to which of the above-mentioned possibilities is correct.

Search for the cause of necrosis in the wall of coronary arteries must take into account the following facts. All instances were observed in infants who were stillborn, or who died shortly after birth (Table I). This points to a causal

CONGENITAL ANEURYSM OF THE RIGHT ANTERIOR SINUS OF VALSALVA (INTERVENTRICULAR ANEURYSM) WITH SPONTANEOUS RUPTURE INTO THE LEFT VENTRICLE

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SSPONTANEOUS rupture into the left ventricle of a congenital aneurysm of the right anterior sinus of Valsalva of the aortic valve is an occurrence heretofore undescribed in the literature. Such a case is herewith presented along with a brief discussion of the condition and of the interesting clinical aspects involved.

CASE REPORT

A. S., a 38-year-old Negro mechanic, was first admitted to Gallinger Hospital on Dec. 2, 1946, with the complaints of swollen feet of three days' duration and cough of two months' duration. He had apparently been perfectly well until the development of a "hacking cough," which was productive of a white, foamy sputum two months prior to admission. This persisted, and one and one-half months before admission, he began experiencing mild dyspnea on exertion which soon became severe and progressed to orthopnea. One month before admission, while working, he experienced a sudden dull midsubsternal pain which radiated to both the right and left upper abdominal quadrants. This pain persisted for several hours and was aggravated by numerous coughing spells. Two and one-half weeks later he began experiencing nausea and vomiting following his coughing spells. A progressive swelling of his feet occurred during the three days prior to his admission.

At the age of 24 years a vague attack of "rheumatism" had occurred. He had had an untreated "penile sore" lasting for two weeks at the age of 28 years. No serologic test for syphilis was performed at that time. During the two years prior to his hospitalization he had been hoarse as a result of undetermined reasons.

Physical examination on admission revealed a chronically ill and orthopneic Negro man, who appeared to be his stated age. The blood pressure was 180/40 to 20; the pulse was 100 per minute and of the waterhammer type; respirations were 24 per minute; and the temperature was 98.6° Fahrenheit. The anterior cervical and inguinal lymph nodes were palpable and small. The neck veins were slightly engorged and pulsating. The respirations were rapid and shallow. Crepitant rales were heard over both lungs. The heart was enlarged. Its left outermost border was 14 cm. from the midsternal line in the sixth anterior intercostal space. The point of maximal impulse was in the fifth left intercostal space at the anterior axillary line. A blowing aortic diastolic murmur was transmitted along the left sternal border to the apex and to the left axilla. A localized, soft, aortic systolic murmur was also described, as were a harsh apical diastolic murmur and a long, soft, apical systolic murmur. The rhythm was regular. The abdomen was moderately distended with bulging in the flanks. There was a questionable fluid wave and a palpable, tender liver which extended downward to the level of the umbilicus. There was 1 to 2 plus pitting edema of the legs, ankles, feet, and sacrum. The remainder of the physical examination, including the neurological, was essentially negative.

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the media of arteries to become apparent than for extravasation of blood from capillaries.

After the examination of the lesions in the coronary arteries was nearly completed, similar changes were found in the arteries of the liver of four newborn infants with normal coronary arteries. Three of them showed marked signs of asphyxia. Renewed examination of the organs of the infants with changes in the coronary arteries revealed similar changes in the liver of two of them (Cases 16 and 18). The evaluation of this observation cannot be attempted until more information is available. So far, no other organ has been found to be affected.

SUMMARY

Necrosis in the media of coronary arteries has been found in twenty-one newborn or stillborn infants or in 9.5 per cent of the autopsies performed on infants up to three days of age. These infants showed various degrees of the common signs of asphyxia, including focal hemorrhages in thoracic and other organs and aspiration of unusually large amounts of vernix caseosa.

The outer part of the media is consistently affected, whereas the inner part is spared in some instances. The intima is intact almost without exception. Small thrombi were found in two cases. Rupture of an artery has not been observed.

The adventitia is the seat of edema and hemorrhage, as it is also found to be in infants with signs of asphyxia but without necrosis. There are indications that necrosis in the media is secondary to a change in the surrounding tissue, and that it may appear only after the latter has reached a certain limit of intensity and duration.

The significance of necrosis in the media of coronary arteries of the newborn infant is not known. As a rule, the vessels in the heart of an asphyxiated infant are greatly dilated, regardless of the presence of necrosis. No healing stages of the lesion have been found. Healing may be complete, or the lesion may be fatal, or terminal.

REFERENCES

1. Kissane, H. W., and Fidler, R. S.: Congenital Medial Sclerosis of the Coronary Artery, *AM. HEART J.* 7:133, 1931.
2. Hori, H., Imai, M., and Sato, M.: On the Electrocardiogram of the Newborn. II. On the Electrocardiogram of the Asphyxiated Newborn, *Jap. J. Obst. & Gynec.* 18:333, 1935.
3. Himwich, H. E., Alexander, F. A. D., and Fazekas, J. F.: Tolerance of the Newborn to Hypoxia and Anoxia, *Am. J. Physiol.* 133:327, 1941.
4. Wilson, J. L., Reardon, H. S., Murayama, M., Graham, B., Tsao, M. U., and Baumann, M. L.: Anaerobic Metabolism in the Newborn Infant. I. On the Resistance of the Fetus and Newborn to Oxygen Lack, *Pediatrics* 1:591, 1948.
5. Gürich: Herzmuskelveränderungen bei Leuchtgasvergiftung, *Münch. Med. Wchnschr.* 72:2194, 1925.
6. Kernohan, J. W., and Woltman, H. W.: Postoperative, Focal, Nonseptic Necrosis of Vertebral and Cerebellar Arteries With Rupture and Subarachnoid Hemorrhage, *J. A. M. A.* 122:1173, 1943.

current in the right arm as compared to that in the left was accompanied by a reduction in the size of the deflections in Lead I.

All of the potential differences between the central terminals, with one exception, were so large that they could not be satisfactorily recorded. The last two strips of record in Fig. 3 show the effect of throwing a millivolt into the electrocardiographic circuit at the beginning of the experiment, and again at the end. The sensitivity of the instrument decreased slightly during the interval which elapsed between the two tests.

DISCUSSION

It is evident that the phenomena described were dependent, in one way or another, upon the absolute and relative magnitudes of the resistances, or other parameters, of the circuits established by connecting one or more central terminals to the electrodes on the limbs. The circuit elements referred to are indicated in the diagram reproduced in Fig. 4. The five electrodes, *A*, *B*, 1, 2, and 3, on each of two extremities are shown, together with the resistances, R_a , R_b , R_1 , and so forth, between them and the internal tissues. The resistances of the internal tissues of the segments of the extremities between the various electrodes and between the *A* electrodes and the poles of the battery E_1 , which represents the open-circuit potential difference between the two extremities, have been assigned the symbols r_a , r_b , r_c , and so forth. To avoid complications the third extremity is not included in the diagram. When it is necessary to distinguish between the circuit elements of one extremity and those of another, we shall use unprimed symbols when referring to circuit elements associated with the right arm, primed symbols for the corresponding elements associated with the left arm, and double-primed symbols for those associated with the left leg. The symbols *A*, *A'*, and *A''*, for example, refer to the *A* electrodes on the right arm, left arm, and left leg, respectively. For the equal resistances in the branches of the central terminal we shall use the symbol *R*.

The circuit diagram of Fig. 4 is very much like that of a Wheatstone bridge, but has three branches connected in parallel instead of only two. These are the branches in which the central terminals lie. It is clear that the voltage drop in each of them is equal to the difference in potential between the nodes *X* and *X'*. The potential of each of the central terminals, with reference to that of either of these nodes, is determined by the ratio of the two resistances (or sums of resistances) which separates the one from the other. The potential of the terminal connected to the two Number 1 electrodes is, then, determined by the ratio $(R + R_1) : (R + R'_1)$; that of the terminal connected to the Number 2 electrodes, by the ratio $(R + R_2 + r_a) : (R + R'_2 + r'_a)$; and that of the terminal connected to the Number 3 electrodes, by the ratio $(R + R_3 + r_c + r_d) : (R + R'_3 + r'_c + r'_d)$. When these three ratios are equal, the three terminals are necessarily always at the same potential, and when any two of them are equal, the potentials of the corresponding terminals are equal. If the two equal resistances *R* are very large in comparison with the differences in magnitude between the members of each of the other pairs of resistances involved, the differences in potential

count was 2.4 million; the hemoglobin was 42 per cent; the white blood cell count 14,500, with a differential count of 65 segmented neutrophils, 17 unsegmented neutrophils, 12 lymphocytes, and 6 monocytes. The platelet count was 248,880. The bleeding and clotting times were normal. A Kline test was negative. The blood pH, serum proteins, calcium, phosphorus, potassium, and sodium levels were normal. Examination of the spinal fluid yielded 31 mononuclear cells and 1 neutrophil. There were 48.5 mg. of protein per 100 c.c., and 87.5 mg. of sugar per 100 cubic centimeters. A 1:1000 tuberculin test was negative.

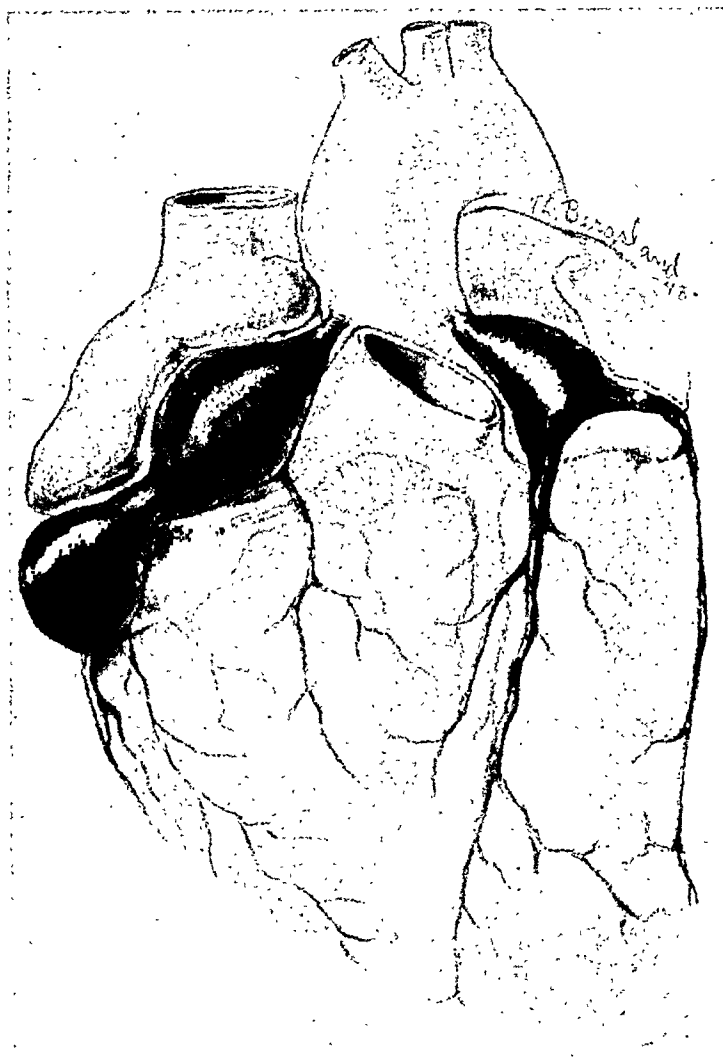


Fig. 1.—Diagram illustrating distribution of aneurysms. The lightly shaded artery is on the posterior wall of the right ventricle.

On the second hospital day the infant developed a faint macular rash over the abdomen. On the following day the rash had spread to the arms and legs and was more pronounced. The conjunctiva became inflamed and the periorbital tissues became swollen. The mucous membranes of the mouth and vulva were markedly hyperemic. The temperature ranged between 39° and 40° centigrade. The white blood cell count rose to 23,000. The rash, conjunctivitis, stomatitis, and vaginitis gradually disappeared after five days, and the swelling in the neck regressed almost entirely. However, the temperature remained elevated and the infant appeared seriously ill. Treatment consisted of penicillin, sulfadiazine, one whole blood transfusion, pheno-

TABLE II. CLINICAL AND PATHOLOGICAL DATA IN TWELVE CASES WITH SEPTUM DEFECTS AND RIGHT-SIDED SUBACUTE BACTERIAL INFECTION

PATIENT	AGE	SEX	HEART	FEVER	LUNGS	BLOOD CUL- TURE	SPLEEN	URINE	KIDNEYS	PETE- CHIAE	ANEMIA	LEUCO- CYTOSIS	SYSTEMIC EMBOLISM	" CLUB- BING	DURA- TION (MONTHS)
Mayer ¹²	16	F	Loud systolic murmur	+	Physical signs; infarcts?		Enlarged; no infarcts	+	No infarcts		+		None	+	6
Tuckwell ²⁰	4	M	Systolic murmur at apex	+	Physical signs; infarcts		Infarct		Negative		+		Left eye; spleen		1
MacKenzie ²¹	21	M	Systolic murmur and thrill		Pain; tuberculosis				Tuberculosis						9
Gordon ⁶	5	M	Loud systolic murmur; thrill	+	Physical signs; infarcts		Enlarged	-		-	+		None		2
Horde ²²	7	M	Loud systolic murmur	+		-		-						+	8
Humphry ²³	18	M	Loud systolic murmur; thrill	+	Physical signs; infarcts	-		+		+		+	None		11
Moschowitz ²⁴	29	F	Loud systolic murmur	+	Pain; hemoptysis; physical signs; infarcts	-	Enlarged; infarcts; hyperplasia; congestion	-	Glomerular nephritis; infarcts	+			Spleen; kidneys		13
Bumgart ⁹	13	F	Systolic and diastolic murmurs and thrills	+	Pain; physical signs; x-ray; infarcts	-	Enlarged; congestion	+	Glomerular nephritis	+	+	+	None		8
Audibert and associates ²⁵	22	F	Loud systolic murmur and thrill	+	Pain; hemoptysis; infarcts	-	Pain; tender; enlarged; infarcts		Congenital deformity		+	+	Spleen		5
Dalous and associates ²⁶	22	F	Loud systolic murmur	+	Hemoptysis; physical signs; infarcts	-	Enlarged; infarcts	+	Negative		+	+	Spleen		5
Eigen and Abel ¹⁷	7	M	Continuous murmur; systolic thrill	+	Negative; x-ray negative	+	Enlarged	-		+	+	+			1
Author, Case 1	13	M	Loud systolic murmur	+	Physical signs; infarcts	+	Enlarged; infarcts	+	Embolic nephritis	+	+	-	Spleen; kidneys		13

tion through the wall in this locus. Attached to the wall in this region was a small amount of adherent, friable, reddish-brown and gray material. At the distal segment the lumen abruptly narrowed to a diameter of 1.0 mm. for a distance of 2.0 millimeters. Distal to this constriction the artery again became dilated and formed a second fusiform aneurysm measuring 15 by 9 millimeters. The wall was similar to that previously described, but was intact. As the artery coursed along the posterior and basal portions of the right ventricle, the lumen gradually dilated, reaching a maximum internal diameter of 4.0 mm., and then gradually returned to normal. This involved a portion measuring 12 mm. in length. The secondary branches of the artery were not remarkable.

The left coronary artery presented a single, similar aneurysm which arose 1.0 mm. distal to the ostium and measured 15 mm. in length and 7.0 mm. in diameter. The proximal portion of the circumflex and left anterior descending arteries was involved for a short distance. The coronary veins were normal. There were no significant gross lesions in other organs.

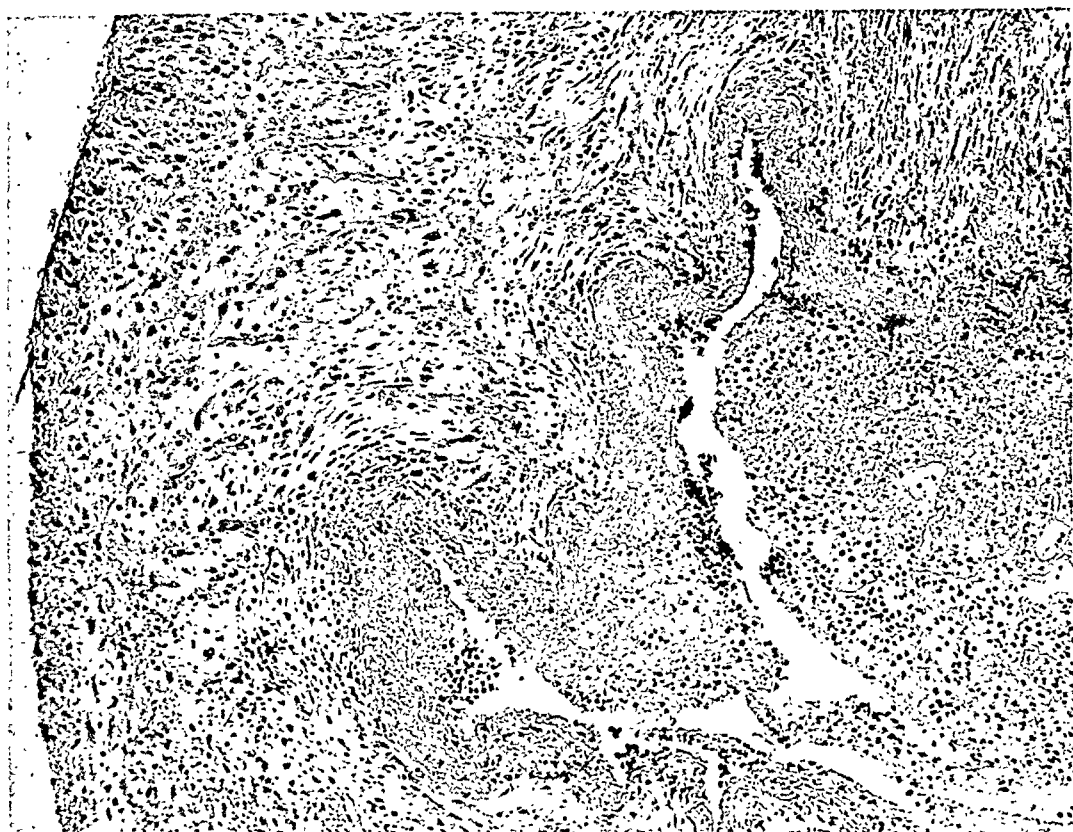


Fig. 3.—Photomicrograph ($\times 102$) of wall of first aneurysm of right coronary artery. Note mural thrombus, variation in thickness of wall, loss of normal pattern, and necrotizing and exudative character of inflammation.

Microscopic studies of the coronary arteries demonstrated involvement of all layers and of the entire circumference of the wall. The intima was replaced by edematous organizing granulation tissue consisting of fibroblasts, mononuclear macrophages, numerous thin-walled vascular channels, a rich infiltration of lymphocytes, eosinophils, and neutrophils, and a few erythrocytes. Deposited upon the surface in many regions was a thin layer of fibrin and granular eosinophilic material enmeshing neutrophils, and into this layer capillaries extended. The internal elastic membrane was not recognizable. The media was almost completely replaced by organizing granulation tissue similar to that already described, which, in addition, contained many more extravasated erythrocytes. In most foci muscle was lacking, while in other regions necrotic muscle was present. The adventitia and adjacent subepicardial fat were likewise involved.

The destruction of the wall was so complete that in many places distinction of the various layers was impossible. In no instance was bacterial colonization evident. The proximal aneurysm of the right artery was perforated. The neighboring intima was the seat of an organizing mural thrombus. The adjacent myocardium was slightly infiltrated with neutrophils and a few lymphocytes, and the epicardium was notable because of focal organizing acute epicarditis. These changes were confined to the main coronary arteries. All other arteries were normal.

Significant anatomic diagnoses were acute and organizing necrotizing exudative arteritis of the coronary arteries morphologically identical with polyarteritis nodosa, multiple aneurysms of the coronary arteries with rupture of the proximal aneurysm of the right coronary artery, organizing mural thrombus of the right coronary artery, hemopericardium, slight focal acute and chronic exudative myocarditis, focal organizing acute epicarditis, slight focal acute interstitial pneumonitis, slight acute bronchitis, and eosinophilic infiltration of the pulp of the spleen.

DISCUSSION

This case is unusual, and worthy of note for several reasons. First, it is the sixth case of polyarteritis nodosa reported in infants under 1 year of age.^{5,7} Second, the disease was confined to the coronary arteries. Third, the polyarteritis nodosa resulted in multiple aneurysms of the coronary arteries, one of which ruptured into the pericardial sac. Fourth, the clinical features of fever, conjunctivitis, stomatitis, vaginitis, an erythema multiforme type of skin rash, and lack of response to sulfonamides and penicillin are suggestive of viral disease and resemble in many ways a mild form of Stevens-Johnson syndrome.⁸ Finland, Jolliffe, and Parker⁹ described four cases of Stevens-Johnson syndrome in which evidence of infection with a psittacosis-like virus was obtained in three patients. None of these patients, however, had polyarteritis nodosa.

The inflammatory character of the reaction clearly distinguishes these lesions from congenital aneurysm of the coronary arteries as described and reviewed by Harris,¹⁰ who attributed this anomaly to deficiency in elastic tissue.

Pickard, Owen, and Dammin⁴ have reported a case similar in many respects to ours. Their patient was a 15-month-old female infant who three months before death had been hospitalized for rash (erythema multiforme), fever, conjunctivitis, and pharyngitis. Three weeks before death the infant developed cardiac failure and died shortly after her second admission to a hospital. Autopsy disclosed healing and healed polyarteritis nodosa of the coronary arteries, multiple aneurysms of the coronary arteries, coronary thrombosis, and myocardial infarction. Scott and Rotondo⁵ reported the finding of aneurysms of the coronary arteries due to polyarteritis nodosa in two white female children, aged 5 years and 9 months, respectively. Rupture with intrapericardial hemorrhage occurred in one and was considered "imminent" in the other. In the older patient, only the coronary arteries were involved, whereas the coronary, renal, hepatic, and uterine arteries were involved in the infant. The clinical features were similar to those of our patient.

Spector⁶ recorded the occurrence of scarlet fever, periarteritis nodosa limited to the coronary arteries, and aneurysms of the coronary arteries with spontaneous rupture and hemopericardium in a 5-year-old white girl. Vance and Graham's¹¹ patient was a 21-year-old Negro man who had widespread periarteritis nodosa complicated by rupture of an aneurysm of the left coronary artery, with fatal intrapericardial hemorrhage.

Since Von Rokitsansky's paper¹² in 1852, and Kussmaul and Maier's¹³ classic presentation in 1866, polyarteritis nodosa has been the subject of extensive study, discussion, and speculation. The protean clinical manifestations have long been recognized. In recent years attention has been focused chiefly on etiology and pathogenesis, with major emphasis placed on the role of hypersensitivity originally suggested by Gruber¹⁴ in 1925. In 1943, Rich and Gregory¹⁵ produced necrotizing vascular lesions in rabbits made hypersensitive to sterile horse serum. These studies were prompted by the observation of polyarteritis nodosa in patients with serum sickness and in those treated by sulfonamide therapy.¹⁶ Their work has been confirmed by Hawn and Janeway,¹⁷ McKeown,¹⁸ and recently by Orbison¹⁹ at this institute. On the other hand, Fox and Jones²⁰ and Smith and Zeek²¹ were unable to produce polyarteritis nodosa even though their rabbits were made hypersensitive. The last-named investigators placed importance upon the role of sharply rising hypertension as a major factor in pathogenesis.

In 1933, Landsteiner and Van der Scheer²² produced specific hypersensitivity to nonantigenic azo dyes by combining these substances with protein. These studies and others cited by them have provided a framework for the recent concept of polyarteritis nodosa as a manifestation of hypersensitivity to sulfonamides,^{15,23,24} iodine,²⁵ thiouracil,²⁶ phenobarbital,²³ and possibly other chemicals which ordinarily are nonantigenic. Karsner²⁷ distinguished polyarteritis nodosa as a primary arteritis distinct from secondary arteritis of bacterial origin, and laid significance upon the presence of eosinophils in the involved tissues.

In the 1920's virus infection was considered by some investigators^{28,29,30} to be a likely causative agent, but no virus has been isolated or established as a factor beyond doubt. We have been unable to find any reports on virus infection as a cause in a review of the literature of the past twenty years, and conclude that this concept has been overshadowed by the prevailing hypothesis of hyperergy. Although the clinical features of our patient suggested a viral origin, we do not propose to imply that this was the case, but merely desire to call attention to the older idea of virus infection as an excitor of this disease. With the newer techniques and the increasing opportunity for the study of viruses, it is anticipated that further investigation of this problem will be forthcoming. Likewise, we believe that in this instance it is impossible to state with any assurance the role played by sulfadiazine and other medication in the production of polyarteritis nodosa.

SUMMARY

A case of polyarteritis nodosa in a white female infant 9 months old is reported. The process was confined to the coronary arteries and was complicated by rupture of an aneurysm with subsequent intrapericardial hemorrhage.

Five similar previously reported cases are summarized. The observations of various investigators pertaining to the role of hypersensitivity to foreign protein, and to the role of sulfonamides and other chemicals which ordinarily are nonantigenic are discussed. The nonbacterial nature of primary arteritis is mentioned. Attention is called to the older hypothesis of virus as an etiological agent. It is not possible in this instance to state what the specific exciting factor was in the production of polyarteritis nodosa.

REFERENCES

1. Keith, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, *J. Pediat.* 18:494, 1941.
2. Rothstein, J., and Welt, S.: Periarteritis Nodosa in Infancy and in Childhood, *Am. J. Dis. Child.* 45:1277, 1933.
3. Stryker, W. A.: Coronary Occlusive Disease in Infants and Children, *Am. J. Dis. Child.* 71:280, 1946.
4. Pickard, C. M., Owen, J. G., and Dammin, G. J.: Aneurysms of the Coronary Arteries Due to Polyarteritis Nodosa Occurring in an Infant: Report of a Case With Coronary Artery Thrombosis and Myocardial Infarction, *J. Lab. & Clin. Med.* 32:1513, 1947.
5. Scott, E. P., and Rotondo, C. C.: Periarteritis Nodosa: Report of Two Cases, One Complicated by Intrapericardial Hemorrhage, *J. Pediat.* 25:306, 1944.
6. Spector, S.: Scarlet Fever, Periarteritis Nodosa, Aneurysm of Coronary Artery With Spontaneous Rupture, Hemopericardium, *Arch. Pediat.* 56:319, 1939.
7. Wilmer, H. A.: Two Cases of Periarteritis Nodosa Occurring in the First Month of Life, *Bull. Johns Hopkins Hosp.* 77:275, 1945.
8. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated With Stomatitis and Ophthalmia, *Am. J. Dis. Child.* 24:526, 1922.
9. Finland, M., Jolliffe, L. S., and Parker, F.: Pneumonia and Erythema Multiforme Exudativum: Report of Four Cases and Three Autopsies, *Am. J. Med.* 4:473, 1948.
10. Harris, P. N.: Aneurysmal Dilatation of the Cardiac Coronary Arteries, *Am. J. Path.* 13:89, 1937.
11. Vance, B. N., and Graham, J. E.: Periarteritis Nodosa Complicated by Fatal Intrapericardial Hemorrhage, *Arch. Path.* 12:521, 1931.
12. Von Rokitsky, C. F.: *Denkschr. d. k. Akad. d. Wissensch. Wein.* 4, 1852. (Cited by various authors.)
13. Kussmaul, A., and Maier, R.: Ueber ein bisher nicht beschriebene eigenthümliche Arterien-erkrankung (Periarteritis nodosa), *Deutsches Arch. f. klin. Med.* 1:484, 1866.
14. Gruber, G. B.: Zur Frage der Periarteritis nodosa mit besonderer Berücksichtigung der Gallenblasen—und Nieren betheiligung, *Virchows Arch. f. path. Anat.* 258:441, 1925.
15. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.* 72:65, 1943.
16. Rich, A. F.: The Role of Hypersensitivity in Periarteritis Nodosa, As Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* 71:123, 1942.
17. Hawn, C. U., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, *J. Exper. Med.* 85:571, 1947.
18. McKeown, E. F.: Experimental Serum Carditis and Its Relationship to Rheumatic Fever, *J. Path. & Bact.* 59:547, 1947.
19. Orbison, J. L.: Personal communication, June, 1948.
20. Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following Administration of a Foreign Protein, *Proc. Soc. Exper. Biol. & Med.* 55:294, 1944.
21. Smith, C. C., and Zeek, P. M.: Studies on Periarteritis Nodosa. II. The Role of Various Factors in the Etiology of Periarteritis Nodosa in Experimental Animals, *Am. J. Path.* 23:147, 1947.
22. Landsteiner, K., and van der Scheer, J.: Anaphylactic Shock by Azodyes, *J. Exper. Med.* 57:633, 1933.
23. Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions Resembling Those of Periarteritis Nodosa and Focal Visceral Necrosis Following Administration of Sulfathiazole, *Am. J. Path.* 22:665, 1946.
24. Goodman, M. J.: Periarteritis Nodosa With Recovery; Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine, *Ann. Int. Med.* 28:181, 1948.
25. Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, *Bull. Johns Hopkins Hosp.* 77:43, 1945.
26. Marine, D., and Baumann, E. J.: Periarteritis Nodosa-like Lesions in Rats Fed Thiouracil, *Arch. Path.* 39:325, 1945.
27. Karsner, H. T.: Acute Inflammations of Arteries, Publication No. 6, American Lecture Series, Springfield, Ill., 1947, Charles C Thomas, Publisher.
28. Von Haun, F.: Patho-histologische und experimentelle Untersuchungen über Periarteritis Nodosa, *Virchows Arch. f. path. Anat.* 227:90, 1919.
29. Harris, W. H.: Etiology and Pathology of Periarteritis Nodosa, *South. M. J.* 19:426, 1926.
30. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, *Am. J. Path.* 6:401, 1930.

COARCTATION OF THE AORTA AT UNUSUAL SITES

REPORT OF TWO CASES WITH ANGIOCARDIOGRAPHIC AND OPERATIVE FINDINGS

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IN A series of twenty-two patients with coarctation of the aorta subjected to angiocardiology before operative treatment, the usual finding by angiocardiology and at operation was a stenosis at the level of the ductus arteriosus. In two instances, however, the coarctation was demonstrated considerably distal to the usual site; in the midthoracic aorta in one patient and below the renal arteries in another. In order to clarify the syndrome associated with such lesions, we present summaries of the histories of these two patients.

CASE REPORTS

CASE 1 (J.H.H. 447239).—B. A., a 35-year-old white woman, was admitted to the surgical service because of hypertension, exertional dyspnea, and numbness and stiffness of the legs. Seven years before admission a routine physical examination had disclosed hypertension. One year later, after running for a bus, the patient suddenly noted numbness and stiffness in both lower extremities. Subsequently the numbness and stiffness of the legs ensued after even mild exercise, and headaches and dizziness were noted. In 1944 the patient underwent bilateral supradiaphragmatic splanchnicectomy with removal of long segments of the greater splanchnic nerves as well as lesser and least splanchnic nerves. The blood pressure in the arms ranged around 230/110 before operation and 195/100 after operation. At that time absence of femoral pulsations was noted, but there was no evidence of collateral circulation and the existence of coarctation of the aorta could not be proved.¹ The headaches and dizziness disappeared, but numbness in the legs persisted. Later the headaches recurred, and in the year before entry the patient developed dyspnea on slight exertion, edema of the ankles, left-sided tinnitus, and transient attacks of amblyopia. She had ten attacks suggesting angina pectoris and began to sleep sitting up in an effort to prevent the severe morning headaches. From her local physician she learned that her blood pressure was slowly rising.

On this admission the systolic blood pressure ranged from 230 to 260 mm. Hg; the diastolic pressure ranged from 110 to 130. No blood pressure readings could be obtained in the lower extremities. There was slight increase in light-streaking of the retinal arteries. The scars of a bilateral paravertebral sympathectomy extended from the level of the sixth thoracic to the second lumbar vertebra. The heart was not enlarged. Over the base a systolic murmur was heard which was transmitted to the neck and back. A soft systolic murmur was heard over the back on either side; this was most intense at the tenth thoracic vertebra, where it became loud and harsh. A similar murmur was heard just below the xiphoid cartilage. Pulsations felt in the epigastrium could not with certainty be differentiated from the forceful cardiac impulse. The radial pulses

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were full and equal; no pulsations were felt in the legs or in the lower abdomen. No unusual vascular pulsations were felt over the chest. A roentgenogram of the chest showed the heart to be of normal size. There was no evidence of notching of the ribs. The urine was normal. Twenty-five per cent of the injected phenolsulfonphthalein was excreted in fifteen minutes and 70 per cent in two hours. An oscillometric test in the left upper arm showed 7.0 mm. of oscillation at a pressure of 170 mm. of mercury. No oscillation could be obtained in either lower extremity.

The patient was admitted with the diagnosis of coarctation of the aorta. There was no doubt that she had aortic obstruction, but the level of the block was thought to be unusual because of the peculiar murmur, the epigastric pulsation, and the absence of collateral circulation in the chest wall despite the patient's age and the hypertension. Angiocardiography was performed with the patient recumbent in the left lateral position. The right ventricle, pulmonary artery, left auricle, and aorta appeared to be normal. There was no evidence of coarctation of the thoracic aorta. A similar injection technique with serial roentgenograms of the abdomen showed complete obstruction of the abdominal aorta at the level of the first lumbar vertebra just

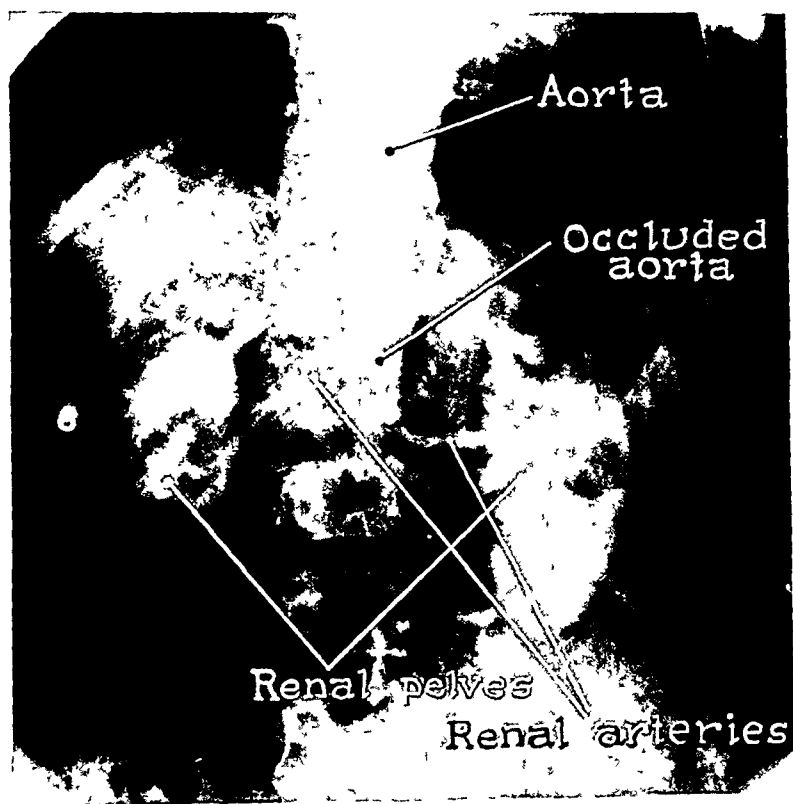


Fig. 1.—Case 1. Visualization of the abdominal aorta by angiocardiographic technique. The renal arteries and the obstruction of the aorta just above them are seen. The renal parenchyma is partially opaque from the Diodrast. Renal pelves are visualized because of a previous injection.

below the origin of the renal arteries (Fig. 1). The renal arteries were demonstrated. The aorta was slightly dilated above the occlusion, and in a conventional film was seen to be slightly more dense than normal, suggesting that there were arteriosclerotic changes. A film taken one second later showed the renal parenchyma to be opaque and of normal size and shape. The renal pelves were filled from the previous injection of Diodrast.

Studies by Bing, Campbell, Handelsman, and Griswold,⁴ with techniques to be described, demonstrated a cardiac output of 3.9 liters per minute per square meter of body surface. Blood flow as measured by plethysmography was 4.6 c.c. per minute per 100 c.c. of tissue in the arm and 1.6 c.c. per minute in the leg. Normal values obtained by this method have ranged from 4.0 to 7.0 c.c. through either extremity. The blood pressure in the right brachial artery was more than 200 mm. Hg systolic and 100 mm. Hg diastolic, with a mean pressure of 144 by direct intravascular

measurement. A ureteral catheter inserted into the left femoral artery was passed to the aortic bifurcation at the level of the third lumbar vertebra. Pressure by direct measurement was 52/45, with a mean of 48 mm. of mercury.

Studies of renal function were performed by Genest using his customary techniques.³ These showed a renal plasma flow of 690 c.c. and a glomerular filtration rate of 178 c.c. per minute per 1.73 square meters of body surface area. The filtration fraction was thus 0.259. This agrees with other investigations demonstrating that hypertensive patients with or without coarctation have evidence of constriction of the efferent arterioles and a resultant increase in the filtration fraction.

On Jan. 16, 1948, Dr. Alfred Blalock performed an exploratory laparotomy. It was thought that if the aortic obstruction were proximal to, or involved the origin of, the renal arteries, an anastomosis of the splenic to the renal artery would be beneficial. The arteries in the rectus abdominis muscles were more prominent than usual. For several inches below the diaphragm the aorta was two to three times normal size. Below this it tapered rapidly to become quite small at about the level of the second lumbar vertebra. Pulsations could not be felt in the arterial tree distal to this area. The lumen of the distal aorta was felt to be patent, but very little blood was flowing through it. The left renal artery was visualized throughout its course and was apparently slightly smaller than normal. The right renal artery was not visualized but could be felt to arise from the aorta just above the obstruction. An attempt was made to denervate the left renal artery by stripping its adventitia. The omentum was placed against the upper surface of the left kidney to aid in collateral circulation. The sympathetic chains together with the second, third, and fourth lumbar ganglia were removed on each side.

The postoperative course was uneventful. The legs were warmer and slight pulsations were felt in the femoral, popliteal, and dorsal pedal arteries. The patient's tolerance for walking was difficult to evaluate but seemed to be slightly improved. She was discharged on the twelfth postoperative day with slight relief from the complaints given on admission.

CASE 2 (J.H.H. 453317).—A. P., a 17-year-old white girl, was admitted to the surgical service because of hypertension discovered in a routine physical examination eight months before. She had noted frequent supraorbital headaches for fifteen months, but these seemed related to eyestrain and decreased in frequency after she stopped school work. She had been otherwise well and had been very active physically throughout her life.

Except for the cardiovascular system, the physical examination was normal. The retinal arteries were seen to be slightly narrowed. The heart was not enlarged; the rate was 100. A harsh, high-pitched, blowing, midsystolic murmur was heard over the entire precordium, loudest, in the second left intercostal space, and transmitted to the vessels of the neck and back. The blood pressure was 180/90 in both upper extremities; it was 145/120 in the left lower extremity and 140/100 in the right lower extremity. Pulsations in the interscapular region could not be felt with certainty. Radial pulses were bounding. Femoral pulses were weak and no pulses could be felt in the distal portions of the lower extremities. Studies of the urine and blood chemistry were normal. Thirty per cent of the injected phenolsulfonphthalein was excreted in fifteen minutes and 75 per cent in two hours.

Unpublished studies by Bing, Handelsman, Campbell, and Griswold showed the brachial arterial pressure to be more than 200 mm. Hg systolic and 100 diastolic. The right femoral arterial pressure was 90/61, with a mean of 78. The cardiac output was 6.7 liters per minute per square meter of body surface. The blood flow in the arm was 4.3 c.c. per minute per 100 c.c. of tissue, and 1.8 c.c. per minute per 100 c.c. of tissue in the leg.

A conventional roentgenogram of the chest showed no definite evidence of notching of the ribs. Angiocardiograms were at first thought to show a narrow band of constriction at the usual site just below the left subclavian artery. Subsequent to surgical exploration this was interpreted as a shadow cast by the bronchus of the left upper lobe (Fig. 2). Several centimeters distal to this point was a long area of narrowing, beyond which the aorta appeared smaller than normal.

On March 10, 1948, Dr. Alfred Blalock performed an exploratory thoracotomy. Incision was made for removal of the fifth rib. A moderate number of collateral vessels were encountered when the incision was made. The arch of the aorta was of normal size. The left subclavian artery was about twice the usual size but was not as large as that usually seen in cases of coarctation. There was no coarctation at the usual site in the region of the ductus arteriosus. However,

several intercostal spaces lower there was diminution in the size of the aorta over a distance of about 4.0 cm., in the center of which the lumen was felt to be quite small. The wall of the aorta in this region appeared to be thickened and indurated, especially on its posterolateral aspect. Distal to the 4.0 cm. area of constriction the aorta increased in size but never reached normal caliber. The intercostal arteries showed remarkably little increase in size. The lung was adherent along the involved segment of the aorta and there was no good plane of cleavage between the aorta and the surrounding tissues. The irregular, pebbly appearance of the aorta suggested an old inflammatory process (Fig. 3).

An attempt at correction of the coarctation would have required a free arterial graft since the area was too far caudad to permit use of the subclavian in the manner described by Blalock and Park.⁴ A partial sympathectomy was performed, with removal of the sympathetic chain and ganglia from the second to the eleventh rib.

The patient's subsequent course was uncomplicated. When discharged from the hospital ten days after operation she was asymptomatic, with a blood pressure in the arms of 145/85.

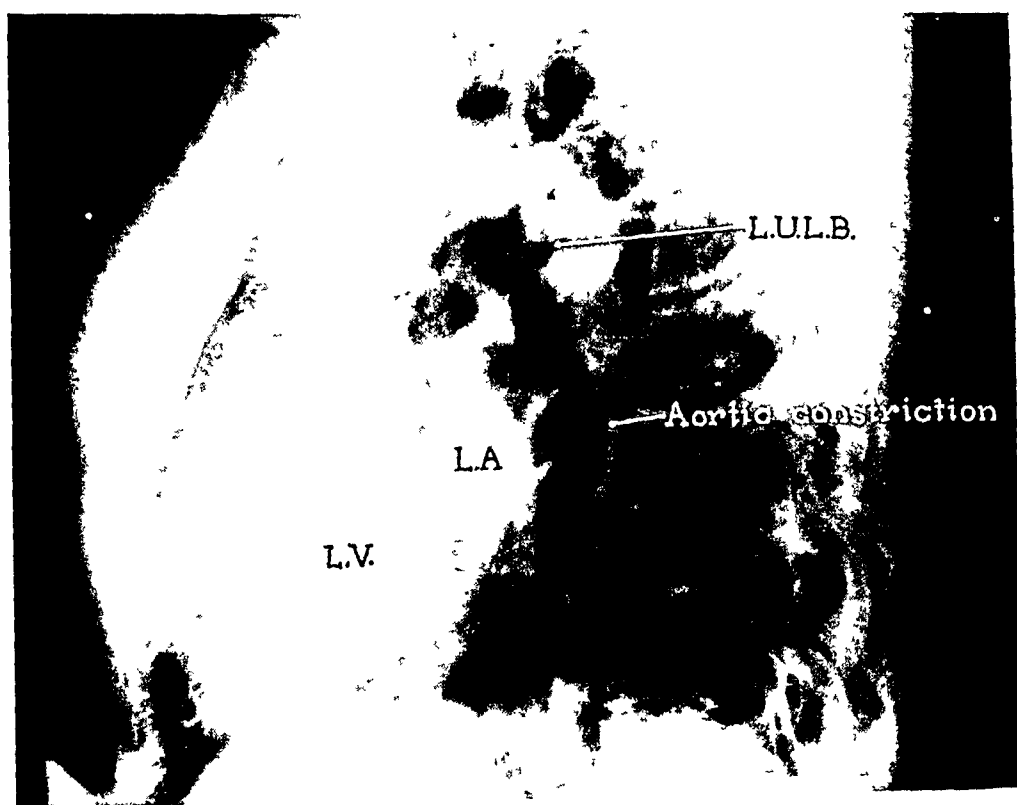


Fig. 2.—Case 2 Angiocardiogram showing the left side of the heart and aorta. The left auricle (L.A.), left ventricle (L.V.), and aorta are seen. The bronchus of the left upper lobe (L.U.L.B.) is responsible for the appearance of a constriction in the isthmus region of the aorta. The actual lesion was below this point.

DISCUSSION

Since the surgical treatment for coarctation of the aorta was introduced independently in 1945 by Crafoord⁵ and by Gross,⁶ the value of such therapy in certain cases has become established. Most cases of coarctation of the aorta fall into two poorly defined groups^{7,8}: (1) The so-called "infantile" type, in which the stenosis is diffuse in the arch of the aorta and customarily between the left subclavian artery and the ductus arteriosus. There are usually significant cardiac defects. Such a condition is almost always incompatible with life for



Fig. 3.—Case 2. Drawing demonstrating the diffuse narrowing below the region of the obliterated ductus arteriosus. The surrounding adhesions are shown.

more than a few days or weeks. (2) The "adult" type, in which the stenosis is localized at or just below the ductus arteriosus, which is partially or totally obliterated. There is usually no other cardiac defect, except possibly a bicuspid aortic valve. Patients with this latter type of aortic defect survive to adult life and are possible subjects for surgical excision of the stenotic area. A rare third type has been described in which the stenosis is below the region of the ductus arteriosus.⁹⁻¹⁹

In recent years there has been increased awareness of this disease on the part of diagnosticians. Though easily diagnosed, it is readily overlooked. The syndrome may include a history of vascular insufficiency in the lower extremities and symptoms of hypertension. The diagnostic signs include absent or diminished arterial pulsations in the lower extremities, a blood pressure lower in the legs than in the arms, evidence of collateral circulation over the thorax, and notching of ribs as seen in the roentgenograms. Although hypertension in the arms and upper part of the body is not invariably present, it is usually a significant feature and not infrequently is the presenting complaint.

These diagnostic observations indicate an obstruction to the flow of blood in the aorta between the vessels to the arms and those to the legs. The level of the obstruction cannot be localized accurately by routine clinical methods. In most patients requiring operation, preoperative determination of the exact site of constriction is not necessary, for it is rare that a patient with the infantile type of this disease reaches adult life or becomes a candidate for operation. Excepting this group of patients, the coarctation in almost all other instances might be assumed to lie in the region of the obliterated ductus arteriosus. However, the two cases described in this report suggest that an accurate localization of the constriction is not only helpful but essential before surgical exploration.

Angiocardiography has been performed in this hospital in an effort to determine before operation the degree and the level of the constriction. Many of these patients have been referred from the Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital. A modification²⁰ of the method described by Robb and Steinberg²¹ has been used. Interpretation of such roentgenograms is often difficult because of the many overlying shadows in the region of the aortic arch, but the degree and the level of coarctation as well as the distance between the origin of the left subclavian artery and the site of constriction can be estimated. It is the latter point which determines the choice between excision of the stenotic area with end-to-end anastomosis and employment of the left subclavian artery to by-pass the coarctation, as described by Blalock and Park.⁴ It is important to know the level of coarctation in selecting the rib for removal since the operative approach should be as direct as possible to avoid dividing more collateral vessels than necessary.

From the available literature we have collected ten cases in which there was an aortic stenosis below the region of the ductus arteriosus. These cases are apparently of two different types; when the stenosis is above the diaphragm the constriction is more diffuse, while the subdiaphragmatic stenoses are usually localized at or just below the level of the renal arteries. Such a classification at present has little significance, although the appearance of the lesion suggests a different etiological basis in the two types.

The first case of stenosis of the thoracic aorta below the region of the ductus arteriosus was reported by Schlesinger⁹ in 1835. In this patient, who died of cardiac failure, the upper aorta was aneurysmal. Just above the diaphragm the aorta was so small as scarcely to allow the passage of a small sound; below the diaphragm the aorta was normal. Hasler¹⁰ in 1911 reported a patient in whom the aorta abruptly became completely obliterated 3.0 cm. above the diaphragm. A fibrous cord 7.0 mm. in diameter replaced the aorta over 2.5 cm. of its thoracic portion. Costa¹¹ in 1931 reported a patient who died following rupture of the first intercostal artery. There was a stenosing diaphragm in the aorta between the first and second intercostal arteries. This is the only recorded case in which the low-lying thoracic stenosis is so sharply localized, and more closely resembles the usual type of coarctation in the isthmus. Also in 1931, Hickl¹² reported a case with cylindrical narrowing of the thoracic aorta just below the isthmus. He attributed this to meso-aortitis but had no proof of the etiological factor. From his description and illustration, the gross pathologic change seems to resemble that in others of this group. Hahn¹³ in 1933 described a patient who died as a result of hypertension and cardiac failure. At the level of the diaphragmatic dome there was a marked constriction through which only a 3.0 mm. sound could be passed. The aorta elsewhere was normal for the age of the patient. Schleckat¹⁴ subsequently reported the same case.

Power¹⁵ in 1861 reported the first case of stenosis of the abdominal aorta below the origin of the visceral arteries. The iliac branches were correspondingly small. Maycock¹⁶ collected all cases reported prior to 1936 and included a patient with protracted amebic dysentery who had brachial arterial hypertension and in whom autopsy demonstrated a complete obliteration of the aorta 1.5 cm. below the origin of the renal arteries. There were gross degenerative changes in the aorta proximal to the stenosis, while below it remained "very delicate and well preserved." Baylin¹⁷ in 1939 described a 32-year-old subject encountered during an anatomic dissection in the course of which complete obstruction of the aorta just distal to the orifices of the renal arteries was observed. He attributed the obstruction to calcification in the walls of aneurysmal dilatations, two of which lay anteriorly just below the renal arteries, with a larger dilatation posteriorly slightly below the first two. The obstruction occurred between the first two and the third, at the level of the second pair of lumbar arteries. Immediately above and below the dilatations there were calcium deposits in the wall, but elsewhere the aorta was completely free of changes.

Steele¹⁸ reported extensive clinical studies performed upon a patient who had hypertension in the arms while the legs showed a low systolic but an elevated diastolic pressure. At autopsy there was constriction of the aorta just above and at the level of the renal arteries. The lumen of the aorta was reduced to about 2.0 mm. in size. Steele¹⁹ has recently studied a patient in whom a thoracolumbar sympathectomy had previously been performed for hypertension. Angiocardiograms made by Dr. George P. Robb showed constriction of the abdominal aorta for about four inches, being immediately below the diaphragm; the aorta and its branches proximal to the isthmus were increased in size, while the isthmus and the descending aorta were uniformly decreased in caliber.

The origin of this condition is obscure, but several theories have been advanced. Hasler¹⁰ felt that the thoracic stenosis was due to an acquired disease but could find no histologic evidence of syphilis, neoplasm, or scar and concluded that an organized thrombus of unknown origin was the cause of the narrowing. Costa¹¹ suggested implants of embryonic aortic arches as the cause of all types of coarctation. He felt that the pre-isthmic stenosis was due to a remnant of the fifth arch; the isthmic type, to a remnant of the sixth; and that which he described just below the first intercostal artery, to a remnant of the right aortic arch. Hickl¹² related the diffuse thoracic stenosis to rheumatic fever but without convincing evidence. He also mentioned syphilis as a possible cause of the stenosis, but the stenosis in each of the other cases he cited was in the isthmic region and the syphilis might have been incidental to the usual type of coarctation. Schlekat¹⁴ felt that the condition was embryologic in origin since he could find no evidence of an inflammatory genesis. Maycock¹⁶ believed that the abdominal stenosis which he described was due to a congenital developmental defect and suggested that the condition might be due to changes involving unequal fusion of the two dorsal aortas with obliteration and loss of one of them.

Relatively little can be said concerning the etiological factors of the two cases reported here when considered in relation to reports which include gross and microscopic pathologic data. There was no history or clinical evidence of syphilis or rheumatic fever in either of these patients. The difference in appearance of the involved areas was impressive. The stenosis in the thoracic aorta was diffuse and the surrounding thickening and irregularity of the aortic wall suggested a low-grade chronic inflammatory change, possibly embryonic or neonatal. The abdominal stenosis, on the other hand, was sharply localized and did not suggest inflammation. It is possible that the thoracic and abdominal aortic stenoses represent the same disease process at different stages in development. The sharp contrast in the anatomic lesions, however, suggests that the pathogenesis of the two conditions is different. In most reported cases of diffuse narrowing the lesion is located in the thoracic aorta, while the abdominal coarctations are more sharply localized. The cases of Costa¹¹ and of Steele¹⁹ provide exceptions to this generalization.

We believe that the abdominal stenosis reported here was of long duration and probably congenital, although the abrupt onset of symptoms related to the deficient circulation of the lower extremities suggested thrombosis of a previously narrowed segment of the aorta. That the abdominal stenosis in our patient could have been secondary to thrombosis or embolism of the aorta was considered, since occlusion without symptoms has been reported.^{22,23} Such patients, however, have suffered from other disease processes which were not present in this patient. The relationship of coarctation to hypertension is not clear, but this patient (B. A.) had hypertension before symptoms of deficient circulation to the legs appeared.

SUMMARY

1. Coarctation at an unusual site in the thoracic aorta of one patient and in the abdominal aorta of another has been demonstrated by angiocardiography and at operation.

2. It is felt that the occurrence of aortic obstruction at such unusual sites, though admittedly rare, nonetheless provides a strong argument for routine use of angiocardiology preliminary to surgical treatment of coarctation.

3. Ten similar cases collected from the literature are reviewed and discussed from the standpoint of the etiological basis. Although proof of any theory is lacking, it is felt that the stenosis in such instances is a congenital lesion.

4. Thoracic and abdominal aortic constriction would appear to have a different though possibly related pathogenesis.

REFERENCES

1. Peet, Max M.: Personal communication, May, 1948.
2. Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E., and Blalock, A.: The Surgical Treatment and Physiopathology of Coarctation of the Aorta, *Ann. Surg.* **128**:803, 1948.
3. Genest, J., Newman, E. V., Kattus, A. A., Sinclair-Smith, B., and Genecin, A.: Renal Function Before and After Surgical Resection of Coarctation of the Aorta, *Bull. Johns Hopkins Hosp.* **83**:429, 1948.
4. Blalock, A., and Park, E. A.: Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta, *Ann. Surg.* **119**:445, 1944.
5. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, *J. Thoracic Surg.* **14**:347, 1945.
6. Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta; Experimental Studies Regarding Its Surgical Correction, *New England J. Med.* **233**:287, 1945.
7. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, The Commonwealth Fund, p. 618.
8. Reifenshtein, G. H., Levine, S. A., and Gross, R. E.: Coarctation of the Aorta. A Review of 104 Autopsied Cases of the "Adult Type," 2 Years of Age or Older, *AM. HEART J.* **33**:146, 1947.
9. Schlesinger: Merkwürdige Verschlüssung der Aorta, *Casper's Wehnschr. f. d. ges. Heilk.* No. 31, p. 489, 1835.
10. Hasler, L. H.: Über einen Fall von Verschluss der Aorta an ungewohnter Stelle. Inaug. Diss., Borna-Leipzig, 1911, R. Noske.
11. Costa, A.: Obliterazione dell'aorta all'imbocco dell'aorta destra; rottura della prima intercostale aortica. Classificazione e patogenesi delle atresie e strettture dell'aorta, *Arch. di pat. e clin. med.* **9**:305, 1930.
12. Hickl, W.: Über zylindrische Aortenverengerung im absteigenden Brustteil infolge von Mesoaortitis, *Frankfurt, Ztschr. f. Path.* **41**:176, 1931.
13. Hahn, M.: Zur Frage tiefsitzender Stenosen der absteigenden Brusttaorta, Inaug. Diss., Berlin, 1933.
14. Schleckat, O.: Angeborene ringförmige Stenose der Aorta descendens in Zwerchfellhöhe, *Ztschr. f. Kreislaufforsch.* **25**:417, 1933.
15. Power, J. H.: Observations on Diseases of the Aortic Valves, Producing Both Constriction of the Aortic Orifice and Regurgitation Through It Into the Left Ventricle, Accompanied With Abnormal Enlargement of the Two Internal Mammary Arteries and Atrophy of Abdominal Aorta and Its Iliac Branches, *Dublin Quart. J. Med. Sc.* **32**:314, 1861.
16. Maycock, W. d'A.: Congenital Stenosis of the Abdominal Aorta, *AM. HEART J.* **13**:633, 1937.
17. Baylin, G. J.: Collateral Circulation Following an Obstruction of the Abdominal Aorta, *Anat. Rec.* **75**:405, 1939.
18. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of Three Cases, *J. Clin. Investigation* **20**:473, 1941.
19. Steele, J. M.: Personal communication, May, 1948.
20. Cooley, R. N., Bahnsen, H. T., and Hanlon, C. R.: Angiocardiology in Congenital Heart Disease of Cyanotic Type With Pulmonic Stenosis or Atresia. I. Observations on the Tetralogy of Fallot and "Pseudo-Truncus Arteriosus," *Radiology* **52**:329, 1949.
21. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man, A Practical Method, *Am. J. Roentgenol.* **41**:1, 1939.
22. Gross, H., and Phillips, B.: Complete Occlusion of the Abdominal Aorta. A Review of Seven Cases, *Am. J. M. Sc.* **200**:203, 1940.
23. Greenfield, I.: Thrombosis and Embolism of the Abdominal Aorta, *Ann Int Med.* **19**:656, 1943.

CONGENITAL MITRAL STENOSIS AND SYSTEMIC RIGHT VEN-
TRICLE WITH ASSOCIATED PULMONARY VASCULAR CHANGES
FRUSTRATING SURGICAL REPAIR OF PATENT DUCTUS
ARTERIOSUS AND COARCTATION OF THE AORTA

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Congenital mitral stenosis is a rare cardiac anomaly. The exact incidence of this lesion is difficult to determine because the terms "stenosis," "atresia," and "aplasia" are not always used in the same sense by different authors. Quoting from Dorland¹ stenosis is "narrowing or stricture of a duct or canal"; atresia is "imperforation, absence, or closure of a normal opening"; and aplasia is "incomplete or defective development of tissue." Both congenital mitral stenosis and atresia are usually associated with aplasia of the left side of the heart and other developmental anomalies. We are presenting a case of congenital mitral stenosis in which the associated defects were all extracardiac, with the exception of right ventricular enlargement, and consisted of hypoplasia and coarctation of the aorta, a large patent ductus arteriosus, and an anomalous coronary artery.

From an extensive review of the literature, Donnally² was able to collect only eleven proved cases of congenital mitral stenosis, to which he added one of his own. In this series hypoplasia of the left side of the heart and enlargement of the right ventricle were the most constantly associated defects. The maximum duration of life was forty-two months. All of the patients developed cyanosis and dyspnea shortly after birth.

Abbott³ in a statistical analysis of 1,000 cases of congenital cardiac disease listed six under mitral stenosis and five under atresia. The commonest defects associated with the former were patent ductus arteriosus, right ventricular hypertrophy, and hypoplasia of the left ventricle and ascending aorta. The oldest patient was 27 years of age.

Farber and Hubbard⁴ described two cases of congenital mitral stenosis occurring in infants 36 and 72 hours old, which they attributed to a "fetal endomyocarditis." Bland, White, and Jones⁵ cast some doubt on an inflammatory pathogenesis by stating that a minimum of two years is probably necessary for the development of any extensive valvular deformity.

Roberts⁶ reported a case in a 20-hour-old infant associated with aortic atresia. He also stated that his was the tenth reported case showing aortic atresia with the usual combination of defects (mitral stenosis, left ventricular

hypoplasia, stenosis of ascending aorta and arch, patent foramen ovale, right ventricular and pulmonary artery dilatation and hypertrophy, enlarged ductus arteriosus, and nonpatent interventricular septum).

Morgan and Sprengel⁷ described a case of *cor biventriculosum pseudotriloculare* in which there was an "anomalous and stenotic mitral valve with cleft aortic leaflet." It is of interest that the patient lived to the age of 60 years.

Jacobius and Moore⁸ reviewed 169 cases of congenital heart disease at the New York Hospital, and classified four as mitral stenosis. Field⁹ listed a similar incidence of this lesion, reporting seven cases of stenosis out of a total of 250 cases of congenital heart diseases. The oldest patient in this series was 1 year and 9 months of age.

Clawson¹⁰ added two more cases of mitral stenosis collected from a group of 141 cases of congenital heart deformities. One of these patients was a stillborn infant and the other died at the age of 9 months.

CASE REPORT

J. S., an 11-year-old white girl, was first seen in the Pediatric Clinic of Colorado General Hospital in August, 1940, complaining of lifelong exertional dyspnea and fatigability, frequent bouts of epistaxis and recurrent attacks of tonsilitis during the preceding six years. The patient's mother stated that she was told that her child had "heart disease" when the infant was 14 days old. The attacks of epistaxis were thought by the child's physician to have been episodes of rheumatic fever and digitalis had been given. There was no past history of chorea, or of cyanosis in the neonatal period. The family history was noncontributory. The patient was admitted for tonsillectomy.

Physical examination revealed slight malnourishment and underdevelopment for a child of 11 years. The temperature, pulse, and respiration were normal. The brachial blood pressure was 130/70. There was questionable cardiac enlargement. Murmurs were described by three different observers as follows: an apical systolic by one; a presystolic by another; and a presystolic with thrill plus a diastolic, both of maximum intensity in the fourth left intercostal space, by yet a third examiner. The extremities showed no evidence of cyanosis or clubbing.

A teleroentgenogram showed a globular-shaped heart with widening on the right and in the region of the thoracic aorta. The electrocardiogram was reported as being consistent with either rheumatic or congenital heart disease on the basis of a prominent P_2 and marked right axis deviation. Laboratory studies revealed a 1 plus albuminuria with an occasional formed element, a red blood cell count of 4.7 million with 14.1 gm. of hemoglobin, and normal bleeding and coagulation times.

Following uneventful tonsillectomy the child was discharged, to be followed in the outpatient department. The diagnosis lay between rheumatic heart disease with mitral stenosis and insufficiency, or congenital heart disease, type undetermined.

The patient was not observed again until July, 1945, when, at the age of 16, she was seen in the Rheumatic Fever Diagnostic Clinic at Colorado General Hospital, having been referred by the school physician. Interval history revealed increasing fatigability and weakness, particularly of the lower extremities, associated with muscle and joint pains but no definite arthritis. Menarche had occurred one year previously and the periods were still irregular.

On this examination the patient was found to be twenty-three pounds under her expected weight. The brachial blood pressure was 130/100. The heart was not enlarged to percussion. The pulmonic second sound was greater than the aortic and accentuated. There was a low-pitched, rough, rumbling systolic murmur of moderate intensity and a brief diastolic murmur, both localized to the pulmonic area. The femoral pulsations were normal and no cyanosis or clubbing of the extremities was noted.

The electrocardiogram was essentially unchanged from that taken five years previously. Cardiac fluoroscopy was of interest. The anterioposterior position demonstrated a tipped-up

apex suggestive of right ventricular enlargement, and a definite increase in the size of the pulmonary artery. The lung markings appeared dense, but no "hilar dance" was noted. In the left anterior oblique position the posterior contour cleared the vertebral column normally. In the right anterior oblique position the left auricle was thought not to be enlarged. Laboratory studies now revealed a polycythemia as manifested by a red cell count of 5.8 million, hemoglobin of 19 Gm., and a hematocrit of 75. The sedimentation rate was normal and the urinalysis showed no abnormality.

The impression at that time was that the patient had congenital heart disease, the most probable lesion being an interauricular septal defect.

She was readmitted to the hospital for further diagnostic studies in October, 1946. She now gave a history of intermittent claudication and also complained of frequent headaches with associated visual disturbances.

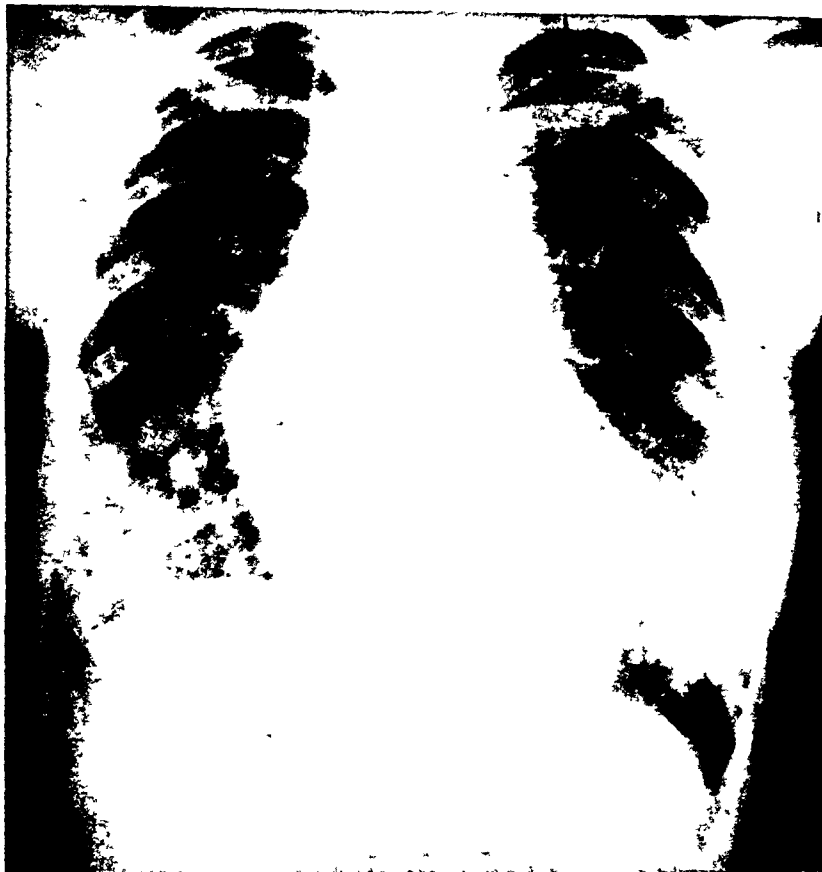


Fig. 1.—X-ray film of the heart and lungs taken Dec. 2, 1947, showing the prominence of the right ventricle, the pulmonary conus, and the congestion of the lung fields

On physical examination it was noted that *the toes were clubbed and cyanotic but the fingers were normal in color and configuration*. The blood pressure was found to be consistently higher in the upper than in the lower extremities with transient rises to hypertensive levels; for example, 129-160/90-118 in the right arm and 105/85 in the right leg. There was marked cupping of the optic discs (later diagnosed as juvenile glaucoma). The lungs were clear to percussion and auscultation. A Grade 3 systolic murmur was heard at the pulmonic area with transmission upward. No diastolic murmur was noted. The liver edge was palpable 3.5 cm. below the right costal margin. There was a palpably enlarged pulsating vessel in the midscapular region. The radial artery pulsations were felt to be stronger than those in the femoral artery.

Laboratory studies again showed a polycythemia with a red blood cell count of 7.1 million and a hemoglobin of 17 grams. Circulation times for arm-to-lung with ether were 5 seconds and 13.5 seconds on two trials; the arm-to-tongue time with Decholin was 21 seconds and 25 seconds on two tests.

Chest x-ray films demonstrated enlargement of the transverse diameter of the heart due mainly to accentuation of the right border, congestive changes in both lung fields, and the presence of a probable azygos lobe. The ribs were not notched. Fluoroscopy of the heart again showed a prominent pulmonary artery and enlarged right auricle and ventricle without demonstrable left auricular enlargement. The electrocardiogram was unchanged. A phonocardiogram showed a late systolic murmur and a split second-sound.

The impression at this point was that the patient had a coarctation of the aorta with an associated interauricular septal defect. Because of postoperative ocular complications, which followed surgery for glaucoma, additional diagnostic studies of her cardiac lesion were not undertaken until a year later, when she was 18 years of age.

For several months prior to readmission to the hospital in September, 1947, the patient had noted increasing dyspnea and orthopnea, together with intermittent pedal edema. She also complained of frequent "fainting spells" which were usually preceded by a feeling of extreme weakness.

The blood pressure in the left arm was 140/120 and in the left leg 120/100. There was a Grade 3 systolic murmur along the left sternal border and a definite diastolic murmur over the pulmonic area. The liver was enlarged 3 to 4 cm. below the right costal margin. By x-ray examination, the contour of the heart was unchanged (Fig. 1).

The percentage oxygen saturation of the arterial blood in the dorsalis pedis artery was 69.3, that in the radial artery was 94.

The possibility of a large patent ductus arteriosus with a right-to-left shunt distal to the coarctation was now considered. As the patient responded well to routine therapy for cardiac decompensation, it was possible subsequently to perform catheterization of the right side of the heart. This procedure was carried out to obtain further evidence on the cardiac circulation with particular reference to the presence or absence of a septal defect. Blood samples and pressure recordings were taken from the right auricle and ventricle and from the right femoral and left brachial arteries. An attempt to advance the catheter into the pulmonary artery was unsuccessful. The pertinent findings obtained from these catheterization studies are shown in Table I.

TABLE I. RESULTS OF CATHETERIZATION AND BLOOD PRESSURE STUDIES

LOCATION	OXYGEN SATURATION (PER CENT)	PRESSURE (STRAIN GAUGE) (MM. HG)
Right auricle	52.6	
Right ventricle	46.2	
Brachial artery	92.1	130/90
Femoral artery	70.2	68/40

From these results it was concluded that the patient did *not* have an interauricular septal defect, and that approximately one-half of the blood in the femoral artery was coming from the right ventricle, presumably through a large patent ductus entering below a coarctation.

The patient's problem was thoroughly discussed in our Chest Conference. There was uniform agreement that the diagnosis was coarctation of the aorta, probably of the infantile type, with a large patent ductus arteriosus entering the aorta distal to it. The abnormal hemodynamics was discussed and most of the consultants felt that the chief strain on the heart was due to the increased load on the right ventricle because of the patent ductus. It seemed apparent that a large percentage of the output of the right ventricle was flowing through the ductus into the aorta at a pressure measured at the femoral artery of 68/40. It was felt that closure of the ductus would tend to remove this strain on the right side of the heart, but at the same time, because of the coarctation, additional strain might be placed on the left ventricle. If repair of the coarctation could be accomplished at the same time, it was hoped that the hemodynamics might be restored to normal. Whether the patient could tolerate occlusion of the aorta during the procedure was questioned, but in the last analysis it was clear that her heart was beginning to fail with increasing rapidity, and her prognosis without surgery was extremely grave.

Preparations for operation were elaborate. Because of the extreme viscosity of her blood (hematocrit of 76) it was felt that less work would be required of her myocardium during operation if the blood were made more fluid. This was accomplished by serial small venesections during the week preceding surgery. Her hematocrit was reduced from 76 to 61, the hemoglobin from 18 Gm. to 15 Gm., and the red cell count from 8.0 million to 6.25 million.

It was felt desirable to be able to evaluate and take immediate corrective measures against any undesirable alterations in her hemodynamics during the operative procedure. A medical-physiological team of five men was present throughout the procedure. With needles in the right radial artery, the right antecubital vein, and the left femoral artery, they were prepared to inject or withdraw blood or fluid from either side of the vascular circuit as indications arose. Constant arterial and venous pressure recordings were taken with the strain gauge. These preparations were made under Avertin anesthesia.

Endotracheal ether anesthesia was begun, and through an anterolateral thoracic incision the mediastinum was entered and the great vessels exposed. A very large pulmonary artery was found from which led a patent ductus arteriosus 2.0 cm. in diameter to the descending aorta. For a distance of about 1.0 cm. above the entrance of the ductus the aorta was extremely small in caliber, perhaps 0.6 cm. in diameter. It was slightly larger, but still definitely smaller than normal (1.0 cm.) between the origins of the left subclavian artery and the left common carotid artery. The first four intercostal arteries were much enlarged. A thrill was palpable in the descending aorta but none in the pulmonary artery *and none over the surface of the heart*. Temporary occlusion of the ductus caused no alteration in the patient's condition as reflected in her chart. It was decided to ligate the ductus as the initial step, with the idea in mind of then proceeding to resection of the coarctation if the patient's condition remained satisfactory. In further freeing the ductus a small tear was made inferiorly which complicated the application of the clamps on the ductus. The hemorrhage was estimated at about 300 c.c. of blood, which was replaced into the femoral artery. Closure of the pulmonary side of the ductus proceeded without event, save that there was an increasing tendency to bleed through the needle holes as we proceeded. It was the operator's impression that the pulmonary artery pressure was rising rapidly during this procedure.

The patient's condition remained quite stable to this point, which was approximately one-half hour after occlusion of the ductus. Respirations, however, suddenly ceased, followed in about one minute with cessation of the cardiac beat. Massage, artificial respiration, transfusion, and stimulants were without avail, and the patient was declared dead. The venous pressure began to rise just before cessation of the heart beat.

Pathologic Findings.—The body was that of a well-developed and well-nourished white girl 18 years of age, measuring 164 cm. (64.5 inches) long and weighing 43.6 kg. (96 lb.). The toes showed advanced clubbing, and the fingers were normal. The autopsy incision was limited to the operative wound of the thorax. The anatomic findings of chief interest were hypoplasia of the aortic arch and coarctation, a ductus arteriosus (Fig. 2), an unusual form of mitral stenosis, an anomalous coronary circulation, and structural changes in the branches of the pulmonary arteries.

The heart weighed about 400 grams and the ventricles were contracted. The left ventricle was normal in size. The right ventricle was hypertrophied so that the two ventricles were approximately equal. The walls measured 10.0 mm. on the left and 9.0 mm. on the right. The left atrium, which was dilated to about twice the normal size, had a wall 5.0 mm. thick. The right atrium was mildly dilated and the wall was slightly hypertrophic. The interauricular septum showed no defect. The mitral valve was unique (Fig. 3). The atrioventricular ring measured 3.0 cm. in diameter. The valve itself consisted of a peripheral shelf of thin gray tissue, 5.0 to 10.0 mm. wide, which showed no trace of the commissures nor the formation of separate cusps. The chordae tendineae were shortened and fused to form a funnel-shaped, firmly fixed, almost solid sheet of tissue that obstructed the orifice of the valve. This anomalous septum was perforated by fifteen scattered slitlike openings, measuring from 1.0 to 5.0 by 2.0 mm. in diameter. The blended chordae were inserted into the apex of the solitary, double-bellied papillary muscle, which arose from the posterior wall of the left ventricle near the margin of the intact interventricular septum. Viewed from above, the mitral valve resembled the inverted top of a salt shaker. The tricuspid, pulmonic, and aortic valves appeared normal.

Microscopically, the epicardium and the endocardium were normal. The myofibers of both ventricles and of the left atrium were enlarged, and the nuclei were plump and vesicular. The interstitial connective tissue was scanty, with no lesions suggesting rheumatic fever. There was no fatty degeneration of the myocardium.

The aorta was thin-walled and the intima was smooth. The ascending aorta measured 2.0 cm. in diameter, but distal to the disproportionately large innominate artery, the aortic arch narrowed to 1.1 cm. in diameter. Distal to the origin of the left common carotid artery, the arch further narrowed to 8.0 mm. in diameter. A segment of the aorta, 8.0 mm. long, and situated immediately distal to the origin of the left subclavian artery, showed coarctation. This segment measured 6.0 mm. in external diameter, and the lumen was completely obstructed at one point by a thin membranous partition. The ductus arteriosus had been completely resected:



Fig. 2.—Photograph of the heart and great vessels. The hypoplasia of the aortic arch, the large pulmonary artery, and the surgically ligated stumps of the patent ductus arteriosus are evident. A, Innominate artery; B, left common carotid artery; C, left subclavian artery; D, coarctation; E, ligated stumps of the patent ductus arteriosus; F, pulmonary artery.

one end opened into the pulmonary artery near the base of the left pulmonary artery superiorly, the opposite end of the ductus entered the descending aorta. Just distal to the area of coarctation and atresia, the descending aorta abruptly expanded to 1.5 cm. in diameter. The enlarged innominate, left common carotid, and left subclavian arteries measured 12.0 mm., 7.0 mm., and 9.0 mm. in diameter, respectively, at the points of origin. The intercostal arteries also were enlarged. The pulmonary artery measured 2.3 cm. in diameter.

Microscopically, the walls of the constricted portion of the aorta and of the pulmonary artery were not different from those of normal great vessels.

The right coronary artery and the anterior descending branch of the left coronary artery arose from normal positions in the sinuses of Valsalva, but the caliber of each vessel was minute and did not exceed 2.0 mm. in the most proximal portions. The left circumflex branch was absent. The most important coronary artery was an anomalous vessel measuring 5.0 mm. in diameter

which originated from the posterior wall of the pulmonary artery near the bifurcation of that vessel. It coursed over the free tip of the left atrial appendage and descended along the left border of the heart to the apex.

Microscopically, the adventitia and media of each coronary vessel appeared normal and the intima was thin.

Grossly, the lungs were dark red, crepitant, and moist. The main interest lay in the microscopic examination. The pleura and interlobular septa were edematous, the alveolar walls were hyperemic, and many of the alveoli contained precipitated edema fluid and macrophages. The



Fig. 3.—Anterior view of the opened left ventricle, showing the funnel-shaped mitral valve cut radially. The few slitlike openings are formed by the irregular fusion of the coarse chordae tendinae which insert on the single papillary muscle.

latter contained no iron pigment. The pathologic alterations of the walls of all of the small arteries and larger arterioles were impressive (Fig. 4). The media showed advanced hypertrophy, and the adventitia was thick and collagenous. Sections stained for elastic tissue demonstrated coarsening and splitting of the internal elastic membrane and extensive proliferation of irregularly arranged elastic fibers throughout the media. Focal areas of the media were also fibrosed. Many of the small arteries exhibited diffuse or eccentric fibrocellular thickening of the intima, with partial obstruction and, in a few instances, obliteration of the lumens. In those arteries showing the

heaviest intimal fibrosis, the elastic tissue in focal areas of the wall was atrophic or absent, while a meshwork of fine and coarse elastic fibers was retained in other areas of the wall. The lumen of a single large artery was almost occluded by an organized mass of connective tissue. The walls of the smallest arterioles were usually thin, but the internal elastic membrane of some was thickened and split.

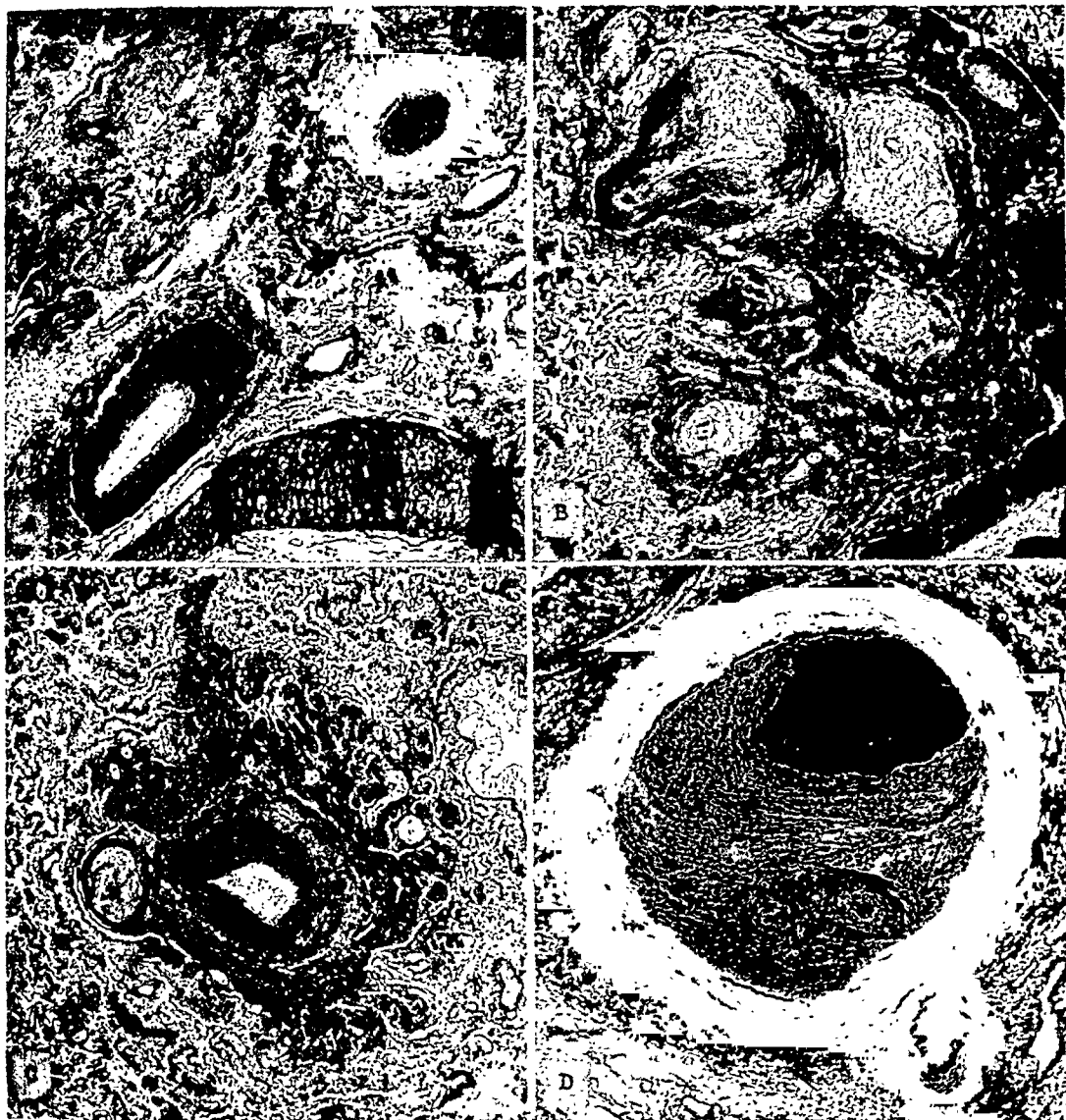


Fig. 4.—Photomicrographs of the pulmonary arterial tree. (Elastic tissue stain, X 60). A, Small arteries showing hypertrophy of the media and hyperplasia of elastic tissue. B, Group of small arteries showing obliterative advanced fibrosis of the wall and irregular distribution of elastic tissue. C, A small artery showing medial and adventitial fibrosis with irregular proliferation of elastic tissue in the media. D, A medium-sized artery showing obstruction of the lumen by organized connective tissue.

DISCUSSION

The left ventricle in this patient appeared normal in size, but the hypoplasia of the aortic arch was severe, and the progressive diminution of the caliber of this vessel, proximal to the opening of the ductus arteriosus, indicated an infantile type of coarctation. The septum traversing the lumen of the aorta in the area of the coarctation completed the obstruction to the flow of oxygenated blood from the arch into the descending aorta. The great vessels branching from the aortic arch were enlarged to accommodate the increased blood flow from the left ventricle into the head and upper extremities, and to supply the only oxygenated blood to the descending aorta via the collateral circulation. If the segment of coarctation had been successfully resected along with the ductus arteriosus, the flow of oxygenated blood to the trunk and lower extremity might not have been greatly improved because of the hypoplasia of the rest of the aortic arch.

The origin of the mitral stenosis was undoubtedly congenital, because gross and microscopic stigmas of rheumatic heart disease or other forms of endocarditis were absent. The term "mitral stenosis" is used, for the want of a more descriptive name, and, furthermore, the valve itself did not resemble that associated with rheumatic fever. The hemodynamics resulting from the obstructive valvular lesion probably differed from the type accompanying rheumatic mitral stenosis in that regurgitation was apparently minimal, while obstruction was apparently as great as was compatible with life.

The changes in the medium-sized and small ramifications of the pulmonary artery were widespread and severe. It is not unlikely that the first alteration in the pathogenesis of these lesions, as suggested by Edwards,¹¹ was hypertrophy of the media of the small vessels. The extensive proliferation of the elastic fibers, the fibrosis of the intima, and the obstruction of the lumen may have occurred subsequently. This is borne out by the comparison of these lesions with those observed by Douglas, Burchell, and Edwards¹² in a child afflicted with what was aptly termed a "systemic right ventricle." The physiologic advantage of the organic changes in the small vessels, in order to maintain the pulmonary hypertension necessary to direct a large proportion of the blood from the pulmonary artery into the descending aorta, is obvious.

Clearly, the ductus arteriosus was a principal outlet for much of the blood leaving the right ventricle, and it was supplying approximately one-half of the blood to the trunk and lower extremities. When the ductus was ligated, the blood which it had previously carried was suddenly channeled into the pulmonary artery. Either the narrowed pulmonary vascular bed or the stenotic mitral valve, or both, were incapable of transmitting the suddenly increased volume. Blood, therefore, was dammed back into the right chambers of the heart; the pressures in the right chambers increased until failure of the myocardium led to death. We believe, from this experience, that in a patient with a systemic right ventricle, conversion of the hemodynamics to normal may be impossible if the changes in the pulmonary vascular bed have progressed to an advanced stage.

In the re-evaluation of this case, we attempted to find a clue which would have led to the preoperative diagnosis of the lesion of the mitral valve. The

physical examination was confusing because the heart murmurs were inconstant, and a murmur diagnostic, or even suggestive, of mitral stenosis was not heard. The fluoroscopic examination failed to reveal the enlargement of the left atrium. The electrocardiographic findings of a prominent P wave and severe right axis deviation were not helpful, as little importance was attached to them in the presence of aortic coarctation and a patent ductus arteriosus. We were unable, in retrospect, to understand how the diagnosis of mitral stenosis could have been established.

Had the diagnosis been made, however, the operation would not have been undertaken. The preoperative rationale of the surgical attempt was based on the opinion that the patient had only two abnormalities, patent ductus and coarctation, both of which individually are amenable to surgical correction. It was then hoped that it might be possible to restore the hemodynamics to normal by correction of the lesions when occurring in this combination. Moreover, observation of the patient's course over the past two years left little room for doubt as to the prognosis if she were not treated.

SUMMARY

The clinical and pathologic findings in a girl 18 years of age suffering from multiple congenital cardiovascular defects are presented. A previously undescribed form of mitral stenosis was associated with coarctation of the aorta and a patent ductus arteriosus. The necessity for establishing the preoperative diagnosis of intracardiac lesions when they are combined with lesions of the great vessels which are potentially amenable to surgical correction is discussed. Of especial importance were the advanced changes in the pulmonary arterial system associated with the systemic right ventricle. Operative restoration of normal hemodynamics may not be possible in the presence of systemic right ventricle if advanced pulmonary vascular changes are present.

REFERENCES

1. Dorland, W. A. N.: *The American Illustrated Medical Dictionary*, ed. 21, Philadelphia, 1947, W. B. Saunders Company.
2. Donnally, H. H.: Congenital Mitral Stenosis, *J. A. M. A.* **82**:1318, 1924.
3. Abbott, M.: Congenital Heart Disease, *Nelson's Loose Leaf Living Medicine* **4**:207, 1931.
4. Farber, S., and Hubbard, J.: Fetal Endomyocarditis: Intrauterine Infection as the Cause of Congenital Cardiac Anomalies, *Am. J. M. Sc.* **186**:705, 1933.
5. Bland, E. F., White, P. D., and Jones, T. D.: The Development of Mitral Stenosis in Young People, *AM. HEART J.* **10**:995, 1935.
6. Roberts, J. T.: A Case of Congenital Aortic Atresia and Hypoplasia of Ascending Aorta, Normal Origin of the Coronary Arteries, Left Ventricular Hypoplasia and Mitral Stenosis, *AM. HEART J.* **12**:448, 1936.
7. Morgan, D. R., and Sprenkel, V.: Cor Biventriculosum Pseudotriloculare, *J. Tech. Methods* **16**:18, 1936.
8. Jacobius, H. L., and Moore, R. A.: Incidence of Congenital Cardiac Anomalies in the Autopsies at the New York Hospital, *J. Tech. Methods* **18**:133, 1938.
9. Field, C. E.: Congenital Mitral Stenosis, *Arch. Dis. Childhood* **13**:371, 1938.
10. Clawson, B. J.: Types of Congenital Heart Disease in 15,597 Autopsies, *Lancet* **64**:134, 1944.
11. Edwards, J. E.: Personal communication.
12. Douglas, J. M., Burchell, H. B., and Edwards, J. E.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case With Obstructive Pulmonary Vascular Lesions, *Proc. Staff Meet., Mayo Clin.* **22**:413, 1947.

Abstracts and Reviews

Selected Abstracts

Mufson, I.: A New Treatment for the Relief of Obliterative Disease of Peripheral Arteries. *Ann. Int. Med.* 29:903 (Nov.), 1948.

By means of a sphygmomanometer and rubber bulb, connected through a Y tube with an infusion burette, the author was able to introduce, under pressure, into the femoral artery in the affected limb a solution of histamine consisting of 1.0 mg. of histamine base in 500 c.c. of normal saline. The dropping rate was measured in the drip indicator during the diastolic fall in pressure during which inflow into the artery took place. It was found that between two and five drops per heart beat permitted an erythema of the thigh to develop without any subjective symptoms. The infusion was given at weekly or biweekly intervals, depending on the severity of the symptoms.

A total of seventeen patients were thus treated. Of this number, thirteen had symptoms of intermittent claudication and four suffered from muscle cramps during sleep. Local alterations of blood flow before and after treatment were predicated upon measurements of skin temperature and the diffusion rate of radioactive sodium over the sole of the foot and the calf following the introduction of 100 microcuries of radioactive sodium into the median basilic vein. Aside from increments in local blood flow, a significant increase in walking tolerance was noted in approximately 80 per cent of those who were disabled because of claudication. The proportions of those with arteriosclerosis obliterans and thromboangiitis obliterans, respectively, are not given. Of the four patients with night cramps, complete abolition of this symptom was accomplished in every instance by three to six weekly infusions of the histamine solution.

The author considers this type of therapy the equivalent of a sympathectomy in a physiological sense and, therefore, recommends its use as a substitute for surgical management of peripheral vascular disease.

WENDKOS.

LaDue, J. S., Murison, P. J., and Pack, G. T.: The Use of Tetraethylammonium Bromide as a Diagnostic Test for Pheochromocytoma. *Ann. Int. Med.* 29:914 (Nov.), 1948.

A benign pheochromocytoma of the right adrenal gland, weighing 298 grams and containing over 8.0 grams of epinephrine, was successfully removed from a 41-year-old man who had suffered from crises of hypertension and episodes of nervousness, palpitation, sweating, throbbing headache, and abdominal pains. Pylelograms had demonstrated downward displacement of the superior pole of the right kidney by an extrarenal mass. The blood cholesterol was 441 mg. and the blood sugar 134 mg. per cent.

Striking elevations of the arterial blood pressure could be induced, prior to operation, by one of the following methods: (a) by having the patient lie on his left side and raise his shoulder by leaning on his left arm; (b) by intravenous injection of 2.0 c.c. of a saline solution containing 0.025 mg. of histamine phosphate; (c) by intravenous injection of a solution containing 400 mg. of tetraethylammonium bromide. The mechanism responsible for the rise in blood pressure, provoked by the last-named procedure is not well understood and is still a matter of conjecture.

WENDKOS.

Bettman, R. B., and Tannenbaum, W. J.: Herniation of the Heart. Ann. Surg. 128:1012 (Nov.), 1948.

The authors report a case of herniation of the heart through a pericardial defect. The pericardial defect resulted from the excision of an adherent piece of parietal pericardium in a patient in whom a pneumonectomy had been performed for carcinoma of the left lung. Following the pneumonectomy the patient was placed on his left side. He immediately went into shock. On reopening of the patient's chest, the heart was found herniated through the pericardial defect. The pericardial rim was slit and the heart was replaced. Recurrence was prevented by removal of practically the entire anterior pericardium. BECK.

Eichna, L. W.: Thermal Gradients During Varying Body Temperatures. Arch. Phys. Med. 29:687 (Nov.), 1948.

The author studied the effect of the application of cold to the skin of patients with non-infectious fever. Patients were divided into two types: Those with a cool, either moist or dry skin; and those with a hot, and usually dry, skin. The author believes that the patient with the hot skin has a good blood flow to the skin and hence presents a good prospect for the lowering of the deep tissue temperature through the application of cooling agents to the skin. The vasoconstricting action of the cold will not be as effective in the case of the patient with a cool skin, since the cutaneous vessels are already vasoconstricted. The author found that even in the presence of cutaneous vasodilatation, cold agents applied to the skin are still likely to produce vasoconstriction and decrease the skin flow to the point where little heat is extracted directly from the blood by the cold. Under such circumstances there was a fall in peripheral tissue temperature with little or no decrease in rectal temperature. Attempts to maintain the cutaneous blood flow during the period of active cooling by friction of the skin were only partially successful in promoting a rapid lowering of rectal temperature during the cooling. The maximum cooling effect was obtained after the cooling agent was removed and the cutaneous circulation returned to its previous level. The author suggests that the most effective method of applying external cold would be in short repeated bouts rather than for long sustained periods.

In unfavorable instances, rectal temperature remains almost unchanged both during and after skin cooling. The vasoconstrictor reflexes initiated by the cool skin may outweigh the central vasodilating influence of the warm blood, and hence the skin remains relatively bloodless, the blood is not cooled, and the deep heat is not extracted. At times the reflexes from the cold skin are so strong that the patient chills and his body temperature may even rise.

ABRAMSON.

Holden, W. D.: Aortic Embolism. Arch. Surg. 57:613 (Nov.), 1948.

After discussing the review of the subject of peripheral arterial embolism made by McClure and Harkins in 1943, the author presents the case history of a 58-year-old man in whom this operation was performed and discusses the autopsy findings in detail.

The early clinical recognition of acute occlusion of the abdominal aorta is not difficult if an examination of the pulses in the lower extremities is performed. The author stresses the importance of early diagnosis and early surgical intervention and discusses the main difficulties encountered in the successful treatment of peripheral arterial embolism.

BECK.

Herring, A. C., and Davis, W. M.: Penicillin Treatment of Subacute Bacterial Endocarditis: Report of Eighteen Consecutive Cases. J. A. M. A. 138:726 (Nov.) 6, 1948.

An analysis is presented of eighteen unselected cases of subacute bacterial endocarditis treated with penicillin during the two-year period of 1944 and 1945. The predisposing cardiac abnormality was rheumatic fever in eleven patients, congenital heart disease in three, and arteriosclerosis in two; in two patients the underlying cardiac lesion could not be determined. In sixteen of the patients the causative organism was the *Streptococcus viridans*; an undifferentiated streptococcus and a pleomorphic streptococcus were isolated in the other two.

Penicillin was administered by either continuous intravenous or continuous intramuscular drip in a total dosage varying from 2,800,000 to 1,114,020,000 units. Heparin was used concomitantly in nine of the patients, three of whom developed febrile and systemic reactions thought to be due to the drug.

The infection was arrested in thirteen of the patients; treatment failures occurred in four patients; and one died during the course of therapy. Ten patients were alive and well one year or more after completion of treatment. All the treatment failures occurred in patients in whom infection had existed for longer than six weeks before therapy was instituted and in those patients in whom the penicillin sensitivity of the causative organism was more than 0.03 unit per cubic centimeter.

The authors point out that the only method of determining the effectiveness of treatment is a period of observation at the end of a course of penicillin. When relapse occurred, evidences became manifest within two weeks following cessation of therapy.

A daily dosage of at least 2,000,000 units of penicillin over a period of six weeks is recommended, and a daily dose of 5,000,000 units or more is advocated if the penicillin sensitivity of the organism is greater than 0.06 unit per cubic centimeter. The routine use of heparin in conjunction with penicillin is not recommended.

HANNO.

Wilson, M. G., and Lubschez, R.: Longevity in Rheumatic Fever: Based on the Experience of 1042 Children Observed Over a Period of Thirty Years. *J. A. M. A.* 138:794 (Nov. 13), 1948.

This paper presents a statistical analysis of the records of 1,042 children with rheumatic fever who were observed over the thirty-year period from 1916 to 1947. Eleven per cent of the patients disappeared from observation during the study. The average length of observation of the 89 per cent who were followed to death or until the end of the study was 14.8 years.

The mean age at onset of the initial rheumatic episode was 6.5 years. During the period of observation, the disease was characterized by active carditis alone in 7 per cent of the patients, by one or more attacks of chorea in 25 per cent, by polyarthritides with or without chorea in 58 per cent, and by active carditis in association with other rheumatic manifestations in 45 per cent. At last observation, cardiac involvement was demonstrable in every patient, and multiple valvular lesions and marked or decided cardiac enlargement were noted in about one-half of the patients. In about one-third of the group the auscultatory signs of valvular lesions regressed during the period of observation. Auricular fibrillation occurred in 4 per cent of the patients; fewer than one-half of the patients with auricular fibrillation survived until the end of the study. Ninety per cent of the group between the ages of 21 and 42 years were able to carry on their normal activity without circulatory embarrassment.

There were 226 deaths, an over-all death rate of 14.7 per 1,000 per year. Rheumatic heart disease accounted for 75.7 per cent of the fatalities and subacute bacterial endocarditis for 10.2 per cent. The over-all incidence of subacute bacterial endocarditis in the entire group was 2.2 per cent. The highest mortality rate took place within one year of onset of the initial attack, and an increased risk occurred at puberty, irrespective of the age at onset. The highest death rates occurred between the ages of 1 and 4 years (33.2 per 1,000) and 10 and 14 years (16.3 per 1,000). There was no significant sex difference in the age-specific mortality rates.

The median duration of life for rheumatic children is greater than thirty years after onset, and the over-all chance to survive to the age of 40 years is one out of two. From the age at onset, the fifteen-year survival rate is 80 per cent, the twenty-year survival rate is 75 per cent, and the thirty-year survival rate is 66 per cent.

HANNO.

Meads, M., Long, R. U., Pace, S. H., and Harrell, G. T.: Caronamide and Penicillin: Serum Levels in Human Beings, Following Multiple Doses of the Drugs. *J. A. M. A.* 138:874 (Nov. 20), 1948.

By virtue of its ability to alter the specific renal tubular enzyme system responsible for the excretion of penicillin, Caronamide (4'-carboxyphenylmethanesulfonanilide), although itself eliminated exclusively by glomerular filtration, retards the excretion of penicillin and enhances and prolongs the concentration of penicillin in the blood.

Seventeen subjects under 60 years of age, none of whom presented evidences of cardiac, renal, or hepatic dysfunction, were given 100,000 units of crystalline penicillin G intramuscularly every four hours for seven days, and Caronamide was simultaneously administered orally every four hours on the second, third, and fourth days. Blood samples were taken for penicillin and

Caronamide concentration determinations on each of the first four days and on the seventh day of the study. Seven of the patients (Group A) received Caronamide in a dosage of 2.0 Gm. every four hours, and ten (five each in Groups B and C) received the drug in rations of 4.0 Gm. every four hours. Determinations of the blood levels of Caronamide and penicillin were made four hours after the administration of the drugs in Groups A and B, and two hours after administration in Group C.

The enhancing effect of a given dosage of Caronamide on the penicillin concentration in the blood varied in different patients in the same group. Three of the seven patients receiving the 2.0 Gm. dose of Caronamide showed no significant increase in the penicillin level as compared with the control periods; in the remaining four patients in Group A intermittent twofold and fourfold increases in the level of penicillin occurred after two or three days of combined therapy. In those subjects receiving Caronamide in doses of 4.0 Gm., a twofold to seventeen fold enhancement of the penicillin level was noted, a greater degree of augmentation being noted two hours after the combined administration (Group C) than four hours after administration (Group B). Maximum penicillin concentrations were achieved after two days of combined therapy. A cumulative effect was noted with Caronamide during the three-day period of administration. The penicillin and Caronamide concentrations in the blood showed generally parallel changes. A blood Caronamide level of 25 mg. per cent was generally required to effect a twofold increase in the penicillin concentration; Caronamide levels exceeding 30 mg. per cent were necessary to increase the penicillin concentration fourfold or more.

No toxic effects from Caronamide were noted in the present study except for nausea in three subjects and vomiting in one. It is pointed out, however, that the toxicity of the drug has not as yet been completely evaluated and that other investigators have reported a rash, evidences of renal damage, and the appearance of a periarteritis nodosa-like syndrome.

Caronamide, because of its penicillin-enhancing effect, will probably prove to be of use in cases where high blood penicillin concentrations are required, such as the treatment of infections due to organisms of low penicillin susceptibility or organisms which have become penicillin resistant.

HANNO.

Rosenburg, M. J.: Subacute Bacterial Endocarditis: Report of a Case of Reinfection.
J. A. M. A. 138:956 (Nov. 27), 1948.

A 31-year-old man was treated for subacute bacterial endocarditis, due to *Streptococcus viridans*, with 800,000 units of penicillin daily for six weeks and apparent cure was effected. After twenty months of good health, he again presented himself with the clinical picture of subacute bacterial endocarditis. Blood cultures again recovered the *S. viridans*, and in vitro tests showed the organism to be sensitive to less than 0.1 unit of penicillin per cubic centimeter. An apical abscess of a molar tooth was found, and culture of the abscess fluid after dental extraction yielded *S. viridans*. The patient was successfully treated with a total of 132,000,000 units of penicillin administered by the intramuscular route, every two hours, over a period of thirty-five days, and he has remained well during a five-month follow-up.

Because of the sensitivity of the causative organism to penicillin in the second attack of endocarditis, the long period of good health between the two episodes, and the presence of an abscessed tooth which apparently served as the site of origin of the second infection, the author believes that the second episode of bacterial endocarditis represented a reinfection rather than a relapse.

HANNO.

Brust, A. A., Assali, N. S., and Ferris, E. B.: The Evaluation of Neurogenic and Humoral Factors in Blood Pressure Maintenance in Normal and Toxemic Pregnancy Using Tetraethylammonium Chloride. J. Clin. Investigation 27:717 (Nov.), 1948.

In a series of twenty-three patients with toxemia of pregnancy and ten normal patients with pregnancies at term studied by the tetraethylammonium chloride (TEAC) "floor" blood pressure responses, it was found that in normal persons at term, the TEAC blood pressure floor is strikingly low and rises to normal levels after delivery. In patients with toxemia of pregnancy the TEAC floor is higher than normal and consistently falls to normal levels after recovery.

Since TEAC is known to eliminate neurogenic tone by blocking the autonomic nervous system at the ganglionic level but has no effect on humoral tone, these results suggest that the hypertension in the toxemia of pregnancy is maintained by an excessive degree of humoral tone. In a normal pregnancy, it is likely that the neurogenic mechanisms are more active than in pregnancy with toxemia.

In general, the height of the TEAC floor parallels the severity of the toxemia. However, there is no evidence that TEAC can differentiate between toxemia and essential hypertension when influenced by pregnancy. It may have diagnostic possibilities in the study of those pregnant patients admitted with borderline elevations of blood pressure. Such patients who have a TEAC response resulting in a diastolic blood pressure floor considerably below 90 mm. Hg would be unlikely to have toxemia.

WAITE.

Stead, W. W., Reiser, M. F., Rapoport, S., and Ferris, E. B.: The Effect of Sodium Chloride Depletion on Blood Pressure and Tetraethylammonium Chloride Response in Hypertension. J. Clin. Investigation 27:766 (Nov.), 1948.

In five patients with benign essential hypertension whose renal function was well preserved, the humoral component of the peripheral resistance (as reflected by the tetraethylammonium chloride "floor") was altered by changes in the salt balance. These patients were able to conserve sodium chloride and maintain a relatively isotonic concentration in the blood even against vigorous attempts at sodium depletion. In seven patients with hypertension who had either severe renal damage or malignant hypertension, the humoral contribution to the elevated blood pressure (the TEAC floor) was not altered by shifting of the sodium balance. In this latter group, a fall of 15 to 20 mEq. per liter of serum sodium concentration was associated with no fall in random pressure or the TEAC floor.

The authors conclude that in some patients with essential hypertension and normal renal function, sodium deprivation tends to decrease the humoral contribution to the maintenance of increased peripheral resistance. In patients with malignant hypertension, renal failure, or both, a large humoral component in peripheral resistance may be uninfluenced by an even greater degree of sodium depletion.

WAITE.

Briggs, A. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.: Renal and Circulatory Factors in the Edema Formation of Congestive Heart Failure. J. Clin. Investigation 6:810 (Nov.), 1948.

A total of thirty-nine patients, twenty-one in congestive failure and eighteen well-compensated, were studied to determine renal and circulatory factors in congestive heart failure. The right heart was catheterized and cardiac output measured. Whole blood volume was determined by the Evans blue dye method instead of by the more customary method of determining plasma volume and interpolating total blood volume from hematocrit. Sodium thiosulfate clearance was used to measure glomerular filtration. Other determinants were the sodium thiocyanate space and serum sodium. It was found that the thiocyanate space was definitely greater in uncompensated than in compensated patients. Furthermore, the kidneys of compensated persons were able to excrete sodium at nearly twice the rate of patients who were uncompensated, although the standard errors of the analyses were large because of the variability of the data. Changes of the blood volume were inconsistent and the averages of the two groups were not different.

The filling pressures of the right ventricle were higher in uncompensated than in re-compensated patients. However, the pressure did not always decrease as compensation was regained nor was there any definite correlation between the height of the pressure and the thiocyanate space. There was little statistical difference between the means of the pressure of both uncompensated and compensated patients. Two patients were in congestive failure with high cardiac outputs. Including these subjects, the average output was higher in the compensated than in the uncompensated, but there was considerable overlapping and compensation was not necessarily accompanied by an increase in output.

Sodium reabsorption correlated closely with filtration rate. The authors explained this correlation by the manner in which the figures are derived; the amount of sodium reabsorbed is calculated by subtracting the quantity eliminated from the amount filtered. Since urinary sodium

is relatively a small quantity, changes here cause negligible changes in the amount filtered. The amount of sodium filtered is obtained by multiplying the plasma level (which is held within narrow limits) by the filtration rate. Thus, plotting sodium resorbed against filtration rate is not unlike plotting *filtration rate against filtration rate times a constant*. However, the ability to excrete sodium consistently improved as the patient regained compensation. These data confirmed the findings of others, that filtration rate in cardiac patients is much less than in normal subjects, but it is emphasized that patients can regain clinical compensation without a significant degree of increase in filtration rate. The ability to excrete sodium always increased after the compensation had been regained.

The determination which bore the closest relation between compensated and uncompensated patients was the oxygen saturation of mixed venous blood. The authors suggest that it is likely that the edema in congestive heart failure is formed from water which cannot be excreted and which is stored in the extravascular spaces. The inability of the kidney to get rid of edema fluid is due to overworking of the mechanism which resorbs salt and water and this in turn seems to be closely related to cellular hypoxia.

They found no support for the observation that an excess of hydrostatic over osmotic pressure in capillaries is a primary factor in the production of edema. Right auricular pressure, though higher than normal, was not consistently higher in the uncompensated than in the compensated patients.

The authors conclude that the circulatory disturbance of congestive failure produces a reduced oxygen tension in the mixed venous blood and that this brings about in some way a more complete resorption of salt and water by the kidneys which in turn is responsible for the edema.

WAIFE.

Salassa, R. M., Bollman, J. L., and Dry, T. J.: The Effect of Para-Aminobenzoic Acid on the Metabolism and Excretion of Salicylate. J. Lab. & Clin. Med. 33:1393 (Nov.), 1948.

The effects of oral administration of para-aminobenzoic acid on the plasma salicylate level and on the urinary excretion of salicylates after oral administration of a single dose of sodium salicylate were studied in both men and dogs. The men were given 3.0 Gm. of sodium salicylate and blood samples were drawn at intervals over the next fifty-six hours. All urine passed during the remainder of the study was collected and the salicyl fractions were determined. When para-aminobenzoic acid was given, its administration was started eighteen hours before the ingestion of salicylate. Para-aminobenzoic acid, 3.0 Gm., was given every three hours for the duration of the study.

The authors found that after a 3.0 Gm. dose of sodium salicylate in men, the plasma salicylate level reached its peak of 18.0 to 22.0 mg. per 100 c.c. in two to four hours and then fell rapidly to 1.0 mg. or less per 100 c.c. in twenty-eight to thirty-two hours. However, when para-aminobenzoic acid was also given, the plasma salicylate level again reached its peak in two to four hours but fell more slowly. They found large quantities of salicyluric acid in the urine after the oral administration of the single dose of salicylate in man. However, when para-aminobenzoic acid was given with salicylates only very small quantities of salicyluric acid were found in the urine in spite of collection of the urine for a period of almost twice as long. There was no retention of salicyluric acid in the blood when it failed to appear in the urine as the plasma salicylate was practically all in the form of free salicylate and only the usual traces of salicyluric acid were present. In dogs the salicylate excretion was found to be much slower than in men and when para-aminobenzoic acid was given the rate of excretion of salicylate was not altered appreciably. Although the principle mechanism by which para-aminobenzoic acid increased the plasma salicylate level and decreased total salicylate excretion appeared to be the interruption of salicyluric acid formation, para-aminobenzoic acid also tended to lower the pH of the urine and this further decreased the total salicylate excretion by decreasing the renal clearance of the free salicylate fraction. When the urine was made strongly alkaline by massive doses of sodium bicarbonate, the clearance of free salicylate fraction increased and the effect of para-aminobenzoic acid was masked. Para-aminobenzoic acid when administered to man appeared to decrease greatly the formation of hippuric acid as measured by the oral hippuric acid liver function test.

KLINE.

Boyd, E. J., and Warner, E. D.: Effect of Vitamin K on Dicumarol-Induced Hypoprothrombinemia in Rats. *J. Lab. & Clin. Med.* 33:1431 (Nov.), 1918.

The purpose of this paper is to report the effect of Dicumarol on the prothrombin level of blood and the modification of that effect by vitamin K. The two-stage method of prothrombin determination was used. This method separates the conversion phase from the clotting phase and thereby eliminates the rate of conversion of prothrombin to thrombin as a factor in prothrombin measurement.

The authors found that when rats were given constant doses of Dicumarol there was a tendency for the animals to develop a tolerance to the drug. After approximately two weeks the prothrombin level tended to rise, and at the end of three to four weeks it commonly approached normal values. In another group of rats the dosage was gradually increased in an effort to keep the prothrombin at a low level. Although the prothrombin level tended to remain low for a longer time, the same effect was noted. Succeeding large doses had less effect than earlier small doses. The authors noted that the maximum hypoprothrombinemic effect of a single large dose of Dicumarol was attained within forty-eight hours and recovery was complete within ninety-six hours after the time of administration of the drug. Vitamin K in large doses had no detectable counteracting effect on the prothrombin level of rats whether given before, during, or after Dicumarol administration.

The authors believe that it is possible that administration of vitamin K affects factors which govern prothrombin conversion as well as those which control its concentration. This would explain the protective action of vitamin K against Dicumarol which has been reported by workers using the one-stage method of prothrombin estimation. It would also explain why this action is not demonstrable by the two-stage method.

KLINE.

Trimble, G. X.: Ventricular Irregularities Induced by Sympatho-Adrenal Discharge and Chloroform. *J. Lab. & Clin. Med.* 33:1438 (Nov.), 1918.

The authors present electrocardiographic studies on dogs in which a sympathoadrenal discharge was pharmacologically induced by the injection of acetylcholine bromide preceded by the injection of atropine and physostigmine salicylate. In this sequence of injections, presumably the muscarinic action of the acetylcholine is blocked by the atropine and the destructive action of cholinesterase on the acetylcholine held in check by the physostigmine, leaving the nicotinic action of the acetylcholine unrestrained. The nicotinic effects of acetylcholine are believed to include a sympathoadrenal discharge and the mobilization of epinephrine or an epinephrine-like substance. Following the series of injections, chloroform vapor was administered and continued uninterruptedly until a danger point was reached, as indicated by marked fall in blood pressure and apnea. Continuous electrocardiograms on Lead II, blood pressure, and respiration records were obtained from the time just prior to the acetylcholine administration until the cessation of the chloroform anesthesia. In six of the nine dogs studied, abnormal electrocardiographic findings were obtained during the reaction to chloroform. These consisted of ventricular extrasystoles, short runs of ventricular tachycardia, a persistent ventricular tachycardia of several minutes' duration, and a ventricular tachycardia changing to fibrillation during which the animal expired. These findings strengthen the suggestion of Chenoweth that intrinsic epinephrine, if liberated in sufficient quantity through emotional stress, could present a serious hazard through its effect on the ventricular complex sensitized to various lipotropic hydrocarbons.

KLINE.

Carson, M. J., Burford, T. H., Scott, W. G., and Goodfriend, J.: Diagnosis of Pulmonary Stenosis by Angiocardiography. *J. Pediat.* 33:525 (Nov.), 1918.

The authors describe their method for obtaining angiocardiograms by the use of the Tautograph, which makes ten radiographic exposures within a period of ten seconds. The normal configuration of the heart chambers and great vessels in the left anterior oblique and anteroposterior positions are presented in a series of figures. The radiograms of four patients with various types of cyanotic congenital heart disease are presented to illustrate the value of angiocardiography in

making the correct diagnosis. The cases presented included a nonfunctioning right ventricle with tricuspid stenosis, persistent truncus arteriosus, tetralogy of Fallot, and Eisenmenger's complex.

The authors feel that angiocardiology may be safely utilized as a diagnostic aid in many cardiac conditions especially in infants and children who are so small that cardiac catheterization is impossible or impractical.

KLINE.

Irwin, H. R., and Winsor, T.: Venous Pressures in Children in Health and Disease. J. Pediat. 33:556 (Nov.), 1948.

The subjects of this study were fifty children between the ages of 3 and 10 years with normal cardiovascular systems, thirteen children with rheumatic heart disease without evidence of congestive heart failure, and four children with glomerulonephritis, none of whom showed evidence of cardiac decompensation. In each subject the venous pressure was determined by the use of a phlebomanometer described by Burch and Winsor. From three to six consecutive readings were taken and the lowest pressure was recorded.

The authors found that in normal children the mean venous pressure between the ages of 3 and 10 years was 54.3 mm. H₂O, with a standard deviation of 17.1. They found that the venous pressure increased slightly with age. In patients with rheumatic heart disease without evidence of congestive failure the mean venous pressure was 92.7 mm. of water. In patients with acute glomerulonephritis the average venous pressure was 97.3 mm. of water.

KLINE.

Lubschez, R.: Immunologic and Biochemical Studies in Infants and Children With Special Reference to Rheumatic Fever. V. Electrophoretic Patterns in Blood Plasma and Serum in Normal Children. J. Pediat. 2:570 (Nov.), 1948.

In this study the electrophoretic patterns of blood specimens from thirty apparently healthy children between the ages of 2 and 11 years are presented. There was no illness for a period of at least four months prior to sampling. The mean values for relative concentrations of the various components are in close agreement with those reported for adults. There were no significant sex differences. In younger children the albumen level was slightly higher and the gamma globulin level slightly lower. A second group of twenty-seven children with a mean age of 4.6 years is also presented. These children had had an illness within four months of the sampling. The illnesses comprised a wide variety of infections. In about 40 per cent of the determinations, there was an elevation of the gamma component. Sampling within a month of the illness produced the greatest number of abnormalities.

JOHNSON.

Wilson, M. G., and Lubschez, R.: Immunologic and Biochemical Studies in Infants and Children With Special Reference to Rheumatic Fever. VI. Electrophoretic Patterns of Blood Plasma and Serum in Rheumatic Children. J. Pediat. 2:577 (Nov.), 1948.

In rheumatic fever the observed increase in the gamma globulin fraction is sometimes offered as additional immunologic evidence of antecedent streptococcal infection, but the effect of antecedent illness has not usually been considered. In a study of the electrophoretic patterns of seventy-nine specimens from forty-two rheumatic children, the results were analyzed with respect to antecedent illness and rheumatic status. The electrophoretic patterns for rheumatic subjects who experienced neither an antecedent infection nor rheumatic fever were within normal limits. Those who developed rheumatic fever but had no antecedent respiratory infection did not demonstrate an increase in the gamma globulin component. Those with an antecedent respiratory infection, but no recurrence of rheumatic fever, showed significant elevations in the gamma component. Likewise, those with rheumatic fever developing subsequent to respiratory illness showed similar elevation of this fraction.

The observations recorded in this study demonstrate that the "elevation of the gamma globulin component is not a function of the rheumatic process but a reflection of previous infection." Apparently the rheumatic and the nonrheumatic subjects have a similar immunologic response to infections presumably streptococcal in origin.

JOHNSON.

Kinmonth, J. B.: Thrombo-angiitis Obliterans. Results of Sympathectomy and Prognosis. *Lancet* 2:717 (Nov. 6), 1948.

The author presents the results of a follow-up study on seventy-seven patients with proved thromboangiitis obliterans. Thrombosis of superficial veins had occurred in twenty-four. The series did not include an unduly high proportion of Jews. The average age of the patients at the onset of the disease was 35 years, the range being 16 to 48 years. The longest period between active episodes was found to be fourteen years. Of the seventy-seven patients, seven died after an average of 9.9 years following the onset of the disease. In each instance the cause of death was related to some type of vascular accident.

The author divided the patients into three groups according to their clinical manifestations. One group consisted of individuals in whom the onset of the disease was in the main vessels, as the femoral or popliteal. In these the predominant symptom was intermittent claudication in the calf, with pronounced postural color changes and wasting of the calf muscles. The collateral circulation was usually adequate to prevent gangrene of the foot and the skin was comparatively healthy. The second group consisted of those patients in whom the smaller vessels were the first to be attacked. Popliteal pulsations were present, but the pulses at the ankle were reduced or absent. The findings consisted of claudication in the sole, rest pain, constant erythrocyanosis of the skin and coldness, followed by ulceration or gangrene of the toes. Some of the patients had intermittent claudication in the calf, which, in the presence of pulsations in the popliteal artery was attributed to obstruction of the muscular branches of the main vessels. The third group consisted of patients with simultaneous involvement of both large and small vessels, with claudication in the calf, rest pain in the foot, and premonitory signs of gangrene.

Of fifty-six patients who had been sympathectomized, improvement in the extremities with regard to intermittent claudication was noted in twenty-five. The best results were found in the group with small vessel involvement. Of 111 patients who had been sympathectomized, the extremities of thirty-seven were amputated while those of seventy-four were preserved. The number of patients not sympathectomized was too small to compare with those on whom this operation was performed. Hence the value of sympathectomy in preserving the limb could not be ascertained. Furthermore, it was difficult to determine whether or not this procedure had any effect on stopping or slowing the progress of the disease. The author was of the opinion that sympathectomy was beneficial with regard to claudication in the sole, rest pain, and the superimposed vasospastic attacks characterized by coldness and numbness. In some of the patients with unilateral Buerger's disease in whom bilateral sympathectomy was performed, the disease subsequently appeared in what had been the sound limb. In other words, prophylactic sympathectomy did not give complete protection from the disease.

ABRAMSON.

Wright, H. P., Osborn, S. B., and Edmonds, D. G.: Rate of Flow of Venous Blood in the Legs Measured With Radioactive Sodium. *Lancet* 255:767 (Nov. 13), 1948.

Radioactive sodium was used to determine the rate of flow of venous blood up the leg in 121 normal people. The subject was placed in the supine position, a gamma-ray counter was arranged so that the screen lay transversely over the femoral vein in the groin, and 1.0 c.c. of the radioactive solution was injected into a prominent vein on the dorsum of the foot as rapidly as possible. Previously, a blood pressure cuff was placed over the ankle and the pressure raised in it to 40 mm. of mercury. The mean time taken for the material to reach the segment of femoral vein covered by the counter was found to be 18 ± 0.9 seconds, with an extreme range of observation of 4 to 50 seconds.

ABRAMSON.

Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis. Valvuloplasty. *New England J. Med.* 239:801 (Nov. 25), 1948.

The authors discuss briefly the historical aspect of the surgical attack on the mitral valve in order to relieve mitral stenosis. The results in the past have been most discouraging.

A discussion is then carried out in regard to three groups of patients who might be benefited by one or another procedure to relieve the circulatory deficiency produced by the mitral stenosis. One of the procedures would be valvuloplasty, an attempt to relieve to some degree the stenosis of the thickened, diseased mitral valve and yet produce relatively minimal insufficiency.

In a second group of patients, there is a relative mitral regurgitation of greater significance than the stenosis, and in these patients, in whom there is a high pressure in the left auricle, the production of an artificial interatrial septal defect might be of value. The authors point out that this operation would not be suitable for patients who have experienced right ventricular failure.

In the third group, patients who are extremely ill and who have attacks of "hypercyanotic angina" are occasionally benefited by removal of the cardiac sympathetic accelerator and afferent nerves. This has been carried out by removal of the inferior cervical ganglion and the first four or five dorsal sympathetic ganglia.

The authors operated upon five patients with mitral stenosis. Two of them were subjected to valvuloplasty, two had atrial septal defects created, and one had cardiac denervation. There was one death and this occurred in the first patient on whom a valvuloplasty had been performed.

The authors point out four principles which they feel are important in the consideration of the surgical management of mitral stenosis:

1. The operation should be performed without dislocation of the heart from the position of optimum function.

2. The button-hole opening of the stenotic mitral valve should be approached from the auricular side so that the funnel directs the cutting instrument to the leaflet margin.

3. Surgical enlargement of the stenotic orifice should be so planned that there is minimal burden from the associated regurgitation (selected insufficiency), and maximum restoration of the valvular function (valvuloplasty).

4. In the presence of mitral obstruction or regurgitation, a rapid heart rate must be avoided; tachycardia tends to increase vascular pressure and is associated with attacks of pulmonary edema or "pulmonary decompensation."

The two patients upon whom valvuloplasty was performed are reported in detail.

LORD.

Palmer, J. L., and Gunderson, S. M.: The Effect of Dicumarol on the Erythrocyte Sedimentation Rate in Normal Men. *New England J. Med.* 239:818 (Nov. 25), 1948.

Because of the dearth of information on the subject, the authors decided to test the effect of the drug on the sedimentation rate of normal persons. Five healthy medical students volunteered as subjects. All were free of a history of liver disease and of significant physical abnormalities.

On completion of these examinations, each subject was put on a daily dose of Dicumarol and daily prothrombin times were determined on the undiluted plasma of each. The prothrombin concentrations were maintained between 10 and 30 per cent of mean normal. The sedimentation rates were determined on twenty-one of the twenty-five days by the use of the Westergren method.

The results of this study indicate that Dicumarol administered in therapeutic dosage for twenty-five consecutive days has no significant effect on the erythrocyte sedimentation rate in normal men. It is possible that the results of this study cannot be applied to the interpretation of the effect of Dicumarol on the sedimentation rates of patients with associated diseases that are known to affect the sedimentation rate.

BELLET.

Gunther, B. S., and Concha, J. B.: A New Method for the Electrical Recording of Mechanical Deformations. *Proc. Soc. Exper. Biol. & Med.* 69:302 (Nov.), 1948.

The authors describe a new electrical method for recording mechanical variations. The method uses the differences in potential obtained by changes in the electrolytic resistance of a glass capillary filled with alcohol and glycerine. They recorded the following tracings obtained in man: (1) the carotid pulse, (2) the jugular pulse, (3) the venous pulse together with the R wave of the electrocardiogram, (4) the radial pulse and the R wave, and (5) the apex beat together with the R wave of the electrocardiogram.

KLINE.

Frisk, A. R., Hammarström, S., Lagerlof, H., Werkö, L., Björkenheim, G., Holmgren, A., and Larsson, Y.: Effect of Tetraethylammonium in Arterial Hypertension. *Am. J. Med.* 5:807 (Dec.), 1948.

Continuing their previous work, the authors have studied the effect of a standardized dose of tetraethylammonium (5.0 mg. per kilogram intravenously) on seventy-one hypertensive patients. The group was divided according to age and height of blood pressure. A comparison was made of the effect of tetraethylammonium upon blood pressure with the spontaneous variability of blood pressure during rest, and the influence of the drug on right auricular, ventricular, and pulmonary artery pressures, cardiac output, and the mean systemic pressure by intra-arterial blood pressure registration.

They found that in younger hypertensive patients without pronounced vascular changes, tetraethylammonium caused a moderate drop in both systolic and diastolic pressures corresponding to the lowest spontaneous value obtained during rest and sleep. In these patients, tetraethylammonium produced the relatively greatest increase in pulse rate. There was a marked lowering of the pressure in the lesser circulation to about one-half of the basic value. In older hypertensive patients with clinical signs of arteriosclerotic changes, tetraethylammonium produced the greatest drop in systolic pressure and relatively the least fall in diastolic pressure. In these cases the decrease in blood pressure fell below the lowest spontaneous value. They also showed the lowest average increase in pulse rate. Thus if administration of tetraethylammonium to a patient with hypertension produces a noticeable fall in systolic pressure and a relatively moderate drop in diastolic pressure simultaneously with a slight increase or decrease in the pulse rate, this is a sign of arteriosclerotic changes, and according to clinical experience, sympathectomy is of less value in these cases. They believe that the test is of some value in selecting patients suitable for operation.

WOODS.

Rosenberg, B., Rosenthal, A. E., and Rosenbluth, M. B.: Effect of the Low Sodium Diet and the Rice Diet on Arterial Blood Pressure. *Am. J. Med.* 5:815 (Dec.), 1948.

This report is based upon observations in nine patients with essential hypertension in which a comparison was made between the findings obtained during the rice diet and during a diet low in sodium but adequate in protein. Each patient was studied in a control period averaging one month directly prior to institution of dietary therapy and for not less than four weeks while on the diet. Studies included blood pressure, urinary output, and blood and urinary sodium.

Case histories were presented and the following conclusions drawn: (1) Urinary sodium on both diets fell to very low levels, but the levels on the rice diet were lower than those on the low sodium diet. (2) Four of seven patients on the low sodium diet experienced a statistically significant fall in blood pressure while three of five on the rice diet did. (3) There was no relief of symptoms despite falls in blood pressure.

The authors believe that these changes are not of sufficiently significant magnitude to warrant the routine use of this type of therapy in the management of essential hypertension.

WOODS.

Steward, H. J., Shephard, E. M., and Horger, E. L.: Electrocardiographic Manifestations of Potassium Intoxication. *Am. J. Med.* 5:821 (Dec.), 1948.

The electrocardiographic manifestations of potassium are reviewed and two cases of potassium intoxication are presented. In these cases auricular standstill and widespread intraventricular block appeared in the electrocardiogram at a time when the serum potassium had risen to a level of 10.0 milliequivalents per liter or higher. In one case the changes followed administration of therapeutic amounts of potassium bicarbonate; in the other the changes occurred spontaneously in the course of the nephrotic stage of subacute glomerulonephritis. The latter represents the first reported case of death from potassium intoxication in the nephrotic stage of subacute glomerulonephritis with only moderate nitrogen retention.

It is recommended that potassium salts be administered with caution if there is any possibility of underlying renal disease. This is pertinent since many of the new salt-substitutes contain appreciable amounts of potassium. Physiological saline solution and hypertonic glucose should be administered intravenously in the treatment of the cardiac manifestations of potassium intoxication.

WOODS.

Book Reviews

TREATMENT OF HEART DISEASE. By William A. Brams, M.S., M.D., Ph.D., Associate Professor of Medicine, Northwestern University Medical School, and Attending Physician, Michael Reese Hospital, Chicago. Philadelphia and London, 1948. W. B. Saunders Company, 195 pages and 9 figures.

In publishing this monograph, Dr. Brams has succeeded in his stated purpose of providing a systematic and practical guide in the treatment of heart disease suitable for the general practitioner and medical student. An excellent review of the pharmacologic action of drugs used in the therapy of heart disease is presented in the first chapter. The discussion of therapy is inclusive, particularly that of congestive heart disease. The wide personal experience and mature judgment of the author is apparent throughout. The book is well written, the format is clear, and the bibliography is adequate.

H. K. HELLERSTEIN, M.D.

CORONARY HEART DISEASE. By A. Carlton Ernestene, M.D. Springfield, Illinois, 1948, Charles C Thomas, Publisher, 95 pages. Price \$2.50.

This is a short monograph covering the entire subject of coronary heart disease from the clinical, electrocardiographic, and roentgenologic point of view. It deals with angina pectoris, myocardial infarction, acute coronary failure, and the complications and sequelae that may arise from these conditions. The book is well written and therefore easily read. Descriptions are excellent since there are no diagrams or figures to illustrate the points brought out. No matter how thoroughly one believes he understands this subject, it will no doubt be found profitable to again review it in this short, concise monograph.

JOSEPH A. WAGNER, M.D.

SUBACUTE BACTERIAL ENDOCARDITIS, Second Edition. By Emanuel Libman, M.D., and Charles K. Friedberg, M.D. New York, 1948, Oxford University Press, 116 pages and 19 figures. Price \$3.50.

This book has been taken from the section on Subacute Bacterial Endocarditis in the Oxford Loose-Leaf Medicine and is a revision of the section published in 1941. The revision has been mainly directed toward the part on therapy. The advent of the new antibiotics, chiefly penicillin, has completely altered the prospects of a patient with subacute bacterial endocarditis. The discussion of their application is well presented in this volume and gives one a clear working knowledge of their uses.

The major part of the book is taken up with a detailed description of the pathology and clinical aspects of subacute bacterial endocarditis. Many original observations and concepts of the authors are presented. These are based on a huge experience with this disease and are, therefore, of great interest and value to any student of internal medicine. One would wish the authors had presented more case material and statistical analyses from their experiences to allow the reader to see how they had arrived at some of their conclusions. This data would have been desirable in the sections on "Mild Cases" and on "Bacteria-free Cases," both of which concepts are usually attributed to the senior of the two authors. They state that nearly all of their mild cases have recovered. This is a remarkable observation in a disease in which spontaneous recovery has always been thought to be rare. One would wish for more details about these interesting cases and further explanations of how they differ from the ordinary cases of this disease which almost never recover spontaneously. Many questions come to mind concerning the concept of the bacteria-free stage. The distinction between recovery and the bacteria-free stage is not a clear one. In the section on prognosis the authors stated that some patients adequately treated with antibiotics go on to die of heart failure or embolization despite the fact that their blood cultures had become negative during treatment. Are these examples of the bacteria-free stage? From the standpoint of analysis of antibiotic therapy it would be important to know whether these patients had recovered from the infection and were suffering from sequelae of the disease or whether they were in an active but bacterial-free stage.

This book, despite some of the questions it leaves unanswered, is a valuable monograph and should be read by all who are interested in subacute bacterial endocarditis.

THOMAS W. CLARK, M.D.

CARDIOPATIAS CONGENITAS DE LA INFANCIA. By Augustín Castellanos y Gonzalez. La Habana, 1948, M. V. Fresneda, 448 pages, 82 figures, and 20 plates. Price \$9.00.

This book is devoted to the study of congenital heart diseases in children. The first part considers the embryology and the physical and technical examination of the heart. The second part discusses cyanosis and the signs of the "blue disease." The third part consists of a detailed study of the various clinical-anatomical syndromes.

Of special value to the cardiologist are the chapters dealing with (1) the development and anomalies of the large veins; (2) the classification of congenital heart diseases on the basis of cyanosis and murmurs; and (3) angiocardiology. The latter technique is studied first as a method; it is then demonstrated in its application to the various diseases and illustrated by excellent sketches. Actual angiocardiology diagrams are presented at the end of the book.

It is to be noted that certain chapters, not based on original studies, are already old; for example, the chapter presenting phonocardiographic data obtained prior to 1937. Other chapters are too brief. It is to be regretted that the author fails to give his personal views on some of the more controversial issues. Several misprints of names somewhat mar the book. The bibliography is limited. A good index is placed at the end.

This book should be useful chiefly to students of angiocardiology, a technique largely developed in children through the widely known work of Castellanos and his School.

A. LUISADA, M.D.

DIRECT ELECTROCARDIOGRAPHY OF THE HUMAN HEART AND INTRATHORACIC ELECTROCARDIOGRAPHY. By Franz M. Groedel, M.D., and Paul R. Borchardt, M.D., F.C.C.P. New York, 1948, Brooklyn Medical Press, Inc., 224 pages, 38 tables, and 29 illustrations. Price \$9.00.

The authors present in detail previously reported results of direct electrocardiographic explorations of the epicardial surfaces obtained from subjects undergoing pneumolysis or pneumonectomy. It is evident from the figures that the electrocardiographic patterns obtained by the authors from auricular and ventricular surfaces during normal activation and during extrasystoles confirm present electrocardiographic concepts. Comparative examinations obtained by simultaneously recording leads from the cardiac surfaces and from the precordium again demonstrate that chest leads may be taken as an adequate representation of cardiac segments subjacent to the exploring electrode. The presentation of this extensive material is of value to those concerned with supplanting empirical knowledge of electrocardiology by factual evidence on spread and distribution of action currents.

The mass of detailed information and an awkwardly written text somewhat obscure the results of relatively simple and valid experiments. The authors have attempted interpretations which are frequently at variance with established electrophysical facts, and the disregard of investigative work outside the orbit of the authors impairs the usefulness of an otherwise interesting monograph.

HANS H. HECHT, M.D.

AN INTRODUCTION TO CARDIOLOGY. By Geoffrey Bourne, M.D., F.R.C.P. Baltimore, 1949, Williams and Wilkins Company, 264 pages and 65 figures. Price \$4.50.

In the words of the author it is the purpose of this book to portray in successive chapters, the chief aspects of cardiovascular disease. The plan of presentation is good and the book is easily read. It contains several statements which may be questioned such as, "Left sided failure is usually the result of mitral stenosis . . ." The discussion of digitalis and digitalis therapy is inadequate even for a book of this type. Too much space is given to certain subjects; for example, the thyroid gland and heart disease. The examination of the heart by x-ray studies is well presented and the illustrations on this subject are well chosen. The discussions on effort syndrome (neurocirculatory asthenia), left submammary pain, and prognosis in myocardial infarction are good. The book has been written for the busy practitioner and the medical student and holds little of interest or value for the internist or cardiologist.

JOSEPH B. VANDER VEER, M.D.

AN ATLAS OF ELECTROCARDIOGRAPHY. By William Dressler, M.D., and Hugo Roesler, M.D. Springfield, Illinois, 1949, Charles C Thomas, Publisher, 503 pages and 439 figures. Price \$14.00.

This book, intended as an aid to those familiar with the fundamentals of electrocardiography, contains nearly 450 electrocardiographic illustrations of excellent technical quality, neatly mounted, and faithfully reproduced. On the facing pages are found the description of each curve, a concise objective diagnosis, the clinical data, and a final comment dealing with the practical application and proper understanding of the observed electrocardiographic changes.

The electrocardiograms illustrating changes from the normal both as to form or rhythm have not been grouped according to etiologic or pathologic conditions, but instead, those curves which display similar "patterns" are arranged together, a system which seems ideally suited to the study of differential diagnosis in an atlas presentation. The summaries which follow each of these groups supplement the atlas with an unusual amount of excellently prepared didactic material. The discussion accompanying the section on unipolar limb leads is particularly worthy of comment; it is a concise, lucid, and reasonable summary of the subject. The plan involves some repetition of material, particularly in regard to myocardial infarction, but on the other hand, often serves to emphasize different aspects.

Because of an unavoidable delay in the publication of the atlas two entire sections, "Advances in the Electrocardiographic Diagnosis of Myocardial Infarction" dealing largely with the newer application of multiple precordial leads, and "Interpretation of the Electrocardiogram with the Aid of Unipolar Limb Leads" were added in order to bring the finished book completely up to date. It is regrettable that this material, particularly that dealing with the unipolar limb leads, could not have been integrated with the presentations of such matters as axis deviation, Q deflections, myocardial infarction, and ventricular hypertrophy. In subsequent revisions it is hoped that this can be done.

The content is uniformly good. Occasionally the authors appear to accept the diagnosis of myocardial infarction rather too readily when the changes in the electrocardiograms are confined alone to the T waves, although usually only after the clinical data have been incorporated in the final interpretation. In the reviewer's opinion too much emphasis has been placed upon the "T₁ less than T₂" pattern as an index of infarction without pointing out that this results simply from the forces which produce a reduction in amplitude or inversion of the T wave in Lead aV_L, a situation present in most cases of anterior infarction or occasionally when the heart is in the vertical position. The section on the normal electrocardiogram could have been greatly strengthened by incorporating a number of records of infants and children taken with complete chest and unipolar limb leads, a subject of considerable general interest at present. These are, however, only minor criticisms of an excellent book.

The index is complete and well organized. It serves to bring together the various parts of a subject which, because of the plan of the book, appear in scattered sections.

Because it has not only the merits of an atlas presentation but also incorporates an unusual amount of teaching material, the book should receive wide acceptance in the study of electrocardiography.

E. M. KLINE, M.D.

RÖNTGENDIAGNOSTIK DES HERZENS UND DER GROSSEN GEFASSE, Second Edition. By Prof. Dr. Erich Zdansky. Vienna, 1949, Springer-Verlag, 434 pages, 5 tables, and 397 figures. Price \$22.00.

This is the second edition of a comprehensive work on cardiovascular roentgenology. Revisions and additions are relatively few, undoubtedly attributable to the author's enforced exile just before and during the war years. An all too brief section of five pages is devoted to angiocardiology; no mention at all is made of electrokymography, a new and important tool available since 1945.

Revisions have occurred in the sections on heart size measurements, derived calculations of heart volume, and the effects of arteriovenous shunts on the heart. New sections include brief discussions on atrophy of the heart, hypertrophy and dilatation, and functional tests utilizing roentgenographic methods.

The portions of the book devoted to the individual chambers of the heart and to the great vessels are authoritative and well and profusely illustrated. This is gratifying for in the following eighty pages the author reverts to the typical configurations in various valvular and nonvalvular affections which have in the past misled both clinicians and roentgenologists. However, even here there is a wealth of data and detail which is worthwhile as a source for references.

Particularly interesting are the sections devoted to constrictive pericarditis, the lungs in chronic passive congestion, to cardiac displacement, and to the aorta in health and disease.

On the whole the book measures up well as a reference volume; it is too discursive and detailed for use as a text. The diagrams and half-tone reproductions are unusually good.

JOHN BERNARD SCHWEDEL, M.D.

CARDIAC CATHETERIZATION IN CONGENITAL HEART DISEASE. By Andre Cournand, M.D., Janet S. Baldwin, M.D., and Aaron Himmelstein, M.D. New York, 1949, The Commonwealth Fund, 108 pages and 17 illustrations. Price \$4.00.

This book, as the authors state in their introduction, deals primarily with the noncyanotic malformations of the heart. It is divided into a general and a special part.

The general section deals with equipment, technique, and with complications of catheterization of the heart in general. This section is also concerned with a general discussion of the characteristic blood pressure tracings obtained and with the formulas used in calculating the various volume flows and shunts in congenital heart disease. Cournand and his co-workers who have done so much to initiate and standardize the technique of catheterization, describe the equipment which is used in their laboratory, i.e., the intravenous catheter, first described in 1941. The authors do not mention more recent types of catheters which permit more rapid sampling of blood. There is also no mention of the use of a stylette within the catheter which gives the tube additional rigidity and makes it easier to guide. The authors use a modified Hamilton manometer and also mention the more popular electric recording devices. Cournand and his co-workers perform catheterization in children under nine years of age under basal Avertin anesthesia. It should be mentioned, however, that in many instances the use of morphine-scopolamine is preferable. Air emboli, venous and intracardiac thrombosis, and cardiac arrhythmias are mentioned as the more frequent complications of catheterization in congenital heart disease. Fortunately, all of these complications are so rare that the combined deaths from cardiac catheterization reported from various laboratories is probably less than 0.1 per cent. Cardiac arrhythmias are undoubtedly the most frequent complications and the advice of the authors to use an electrocardiogram in conjunction with intracardiac catheterization is well given. The pressure recordings are excellent. The illustrations of characteristic tracings from the right and left auricle, right and left ventricle, the pulmonary artery, and the aorta should be of greatest value to all those who are interested in the diagnosis of congenital heart disease by physiological methods. Formulas for the calculation of the various volume flows and shunts are similar to those used by other workers in this field.

The second part of the book deals with specific malformations of the heart and great vessels. Of particular value is the correlation of clinical, roentgenological, and physiological findings. By detailed description of the findings in individual cases, the authors are able to establish patterns which exist in the more typical forms of congenital heart disease. Some of the more common malformations are subdivided according to differences in the hemodynamics (i.e., pulmonary artery pressure). This is of the greatest importance since it stresses the fact, which has been so often overlooked in the past, that a similarity in gross pathology is often associated with a great variety of physiological and therefore clinical findings.

The book represents a great contribution to a rapidly progressing branch of medicine and surgery. It should be considered essential by all those who plan to apply catheterization of the heart as a diagnostic tool in the study of congenital heart disease.

RICHARD J. BING, M.D.

CORONARY ARTERY DISEASE. By Ernst P. Boas, M.D., and Norman F. Boas, M.D. Chicago, Ill., 1949, The Year Book Publishers, Inc., 309 pages and 88 illustrations. Price \$6.00.

Except for the therapeutic use of anticoagulants, comparatively little that is new has appeared during the past few years relating to the clinical aspects of coronary heart disease. In this com-

compact book, the Boases have given a good summary of current knowledge. The senior author for many years has been interested in this subject and has contributed to the literature concerning it. He is, therefore, in a position to express critical opinions concerning controversial matters. The arrangement of chapters has resulted in some unnecessary repetition. Coronary insufficiency is disposed of with relative brevity. Consideration of treatment is adequate and the use of various drugs is discussed in the light of their pharmacologic action according to the best evidence available. Westsal is recommended as a salt substitute although it has recently been condemned because of the toxic effects of lithium. Probably the book was in press before these unfortunate clinical experiences were published.

The chief criticism, in the opinion of this reviewer, is the lack of logical sequence in the presentation of the material. Arteriosclerosis is the main cause of coronary heart disease. Coronary insufficiency, occlusion, thrombosis, and cardiac infarction are episodes in the evolution of this process. Congestive heart failure is the result of the damage to the myocardium. This is a simple concept and upon an understanding of it, rests rational therapy.

An adequate bibliography of some 400 key references is given. The style is clear and the publishers have creditably performed their part. In the words of the authors, "the book is designed as a useful tool for the practicing physician, but the presentation is sufficiently detailed to make it of interest to the cardiologist as well."

ROBERT L. LEVY, M.D.

SHOCK AND ALLIED FORMS OF FAILURE OF THE CIRCULATION. By H. A. Davis, M.D., C.M., F.A.C.S. New York, 1949, Grune and Stratton, 595 pages, 55 figures, and 17 tables. Price \$12.00.

The advances made in the definition and treatment of shock during recent years as well as the scattered studies which preceded the concentrated effort made in World War II have long been in need of, and at last been given, a unified presentation. So great has been the need that it is curious that books such as this do not abound. One reason is the diversity of opinion among potential authors, the need for a penetrating analysis of an extensive literature, and the fact that few have the ability or interest to compass all the phenomena incident to shock, recovery therefrom, and "allied forms of failure of the circulation."

This book opens with a historical review and proceeds through definitions to consider the pathogenesis of shock (physiological, biochemical, and histological), the special types of circulatory failure (adrenal, infectious, obstetric, burn, and anesthetic), and the treatment of each. In so doing, the author demonstrates his familiarity with the field, which he carefully documents. He does not pretend to a magisterial or dogmatic conclusiveness. Rather, he achieves an unusual and refreshing impartiality in the evaluation of the work of others. The objection may be raised that he seems at times to devote disproportionate space to his own observations. This is not a serious objection to the book as a whole. In common with most who have labored in this vineyard, we note also that (according to our lights) not enough is made of arterial transfusion, elective hypotension, and so on. But, in general, the treatment is comprehensive and exact.

Thus, what needed doing, has been done well. The technical makeup is satisfactory. The book can be recommended to all who have to deal with shock and injury, both experimentally and clinically.

I. H. PAGE, M.D., AND A. C. CORCORAN, M.D.

FUNDAMENTALS OF INTERNAL MEDICINE. By Wallace M. Yater, M.D. Third Edition. New York, 1949, D. Appleton-Century-Crofts Company, Inc., 1,451 pages and 315 figures.

The third edition of this popular text, retaining its original concept, covers the vast field of internal medicine with simplification, conciseness, and elimination of theoretical and redundant material. The first 190 pages of the volume outline the essential features of diseases of the heart and blood vessels and form the basis of this review.

Most of this section is again the work of the senior author. The discussion of the diagnosis and treatment of the various etiologic types of heart disease reflects his rich clinical experience. A new and enlarged article on electrocardiography by Dr. Joseph M. Barker brings this subject

up to date. In keeping with the goal of the textbook, a surprisingly large amount of information is contained here. Following a clear presentation of the fundamentals of a rapidly growing subject, the precordial leads are described and evaluated. The unipolar leads, including augmented unipolar extremity leads, are also discussed.

In the opinion of this reviewer, few textbooks of medicine contain as much new information on various aspects of the subject of cardiovascular disease as the present edition of Dr. Yater's *Fundamentals of Internal Medicine*.

WILLIAM G. LEAMAN, JR., M.D.

A PRIMER OF ELECTROCARDIOGRAPHY, Second Edition. By George E. Burch, M.D., and Travis Winsor, M.D. Philadelphia, 1949, Lea & Febiger, 245 pages, 265 illustrations, and 6 tables. Price \$4.50.

This small volume continues to be, in the opinion of the reviewer, the best textbook on electrocardiography now available because, as the authors state in the preface to this second edition, "Re-emphasized is the need for understanding the mechanisms by which electrocardiographic patterns are developed rather than memorizing the patterns and interpreting them empirically."

Except for a number of minor criticisms of no great practical importance, the first two chapters, outlining the fundamental principles upon which electrocardiographic diagnosis should be based, are excellent. As examples of the matters which troubled the reviewer, consider first the statement at the bottom of page 59, "Overshooting is produced by a loose string." This type of artifact is due, not to a loose string, but to a condenser-like action occurring beneath the electrodes and is rarely seen with the metal plates, properly applied with electrode paste, now in general use. A string that is too loose is usually over-damped and cannot respond to quick deflections, which may be greatly decreased in size or disappear entirely. Again on page 87 in the section headed *Right Axis Deviation*, it is stated that, "such disease states as . . . interventricular septal defect, patent ductus arteriosus, . . . are commonly associated with the electrocardiographic picture of *right axis deviation*." This is not true of these two conditions. As a matter of fact, on pages 193 and 194 in Chapter V, it is made clear that right axis deviation does not occur with a simple patent ductus arteriosus. The reviewer has always considered the use of the terms right and left ventricular strain as electrocardiographic double talk and is sorry to see them used so freely in this volume.

The expanded chapter on precordial leads which includes a fairly extensive discussion of the unipolar extremity leads is excellent as are the final chapters on the cardiac arrhythmias and clinical applications of the electrocardiogram. The latter section includes a fairly detailed and entirely lucid discussion of the ventricular gradient.

Finally, the statements at the end of the volume pointing out the limitations of usefulness of electrocardiograms and urging conservatism in their interpretation must be applauded.

F. D. JOHNSTON, M.D.

Acknowledgement of Books Received but not Reviewed

COLLATERAL CIRCULATION (ANATOMICAL ASPECTS) By Daniel P. Quiring, Ph.D., Head of the Anatomy Division, Cleveland Clinic Foundation, and Associate Professor of Biology, Western Reserve University. Philadelphia, 1949, Lea & Febiger, 142 pages. Price \$5.00.

CLINICAL CASE-TAKING. GUIDES FOR THE STUDY OF PATIENTS. HISTORY-TAKING AND PHYSICAL EXAMINATION OR SEMIOLOGY OF DISEASE IN THE VARIOUS SYSTEMS, Fourth Edition. By George R. Herrmann, M.D., Ph.D., Professor of Medicine, University of Texas. St. Louis, 1949, The C. V. Mosby Company, 240 pages.

ON MYOGLOBIN AND ITS OCCURRENCE IN MAN. By Gunnar Biorck. From the Biochemical Department of the Medical Nobel Institute, The Cardiac Clinic of Sodersjukhuset, and the Department of Pathology at Sodersjukhuset, Stockholm, Sweden. Stockholm, Sweden, 1949, Supplement CCXXVI (226), Acta Medica Scandinavica, 216 pages.

SOME SUPPLEMENTARY LEADS IN CLINICAL ELECTROCARDIOGRAPHY. By Karl Erik Grewin. Stockholm, Sweden, 1948, Ivar Haeggstroms Boktryckeri A. B., 463 pages, 142 figures and 50 tables.

American Heart Association, Inc.

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Telephone Plaza 7-2045

ANNUAL MEETING

The Annual Meeting and Twenty-Third Scientific Session of the American Heart Association will be held at the Fairmont Hotel, San Francisco, June 22-25, 1950. All those desiring to attend should make room reservations at the earliest possible date.

PROGRAM COMMITTEE

The Chairman of the Program Committee for the Annual Scientific Session is Doctor Louis E. Martin, 1136 West Sixth Street, Los Angeles 14, California. All who desire to present papers at the meetings in San Francisco should forward to Doctor Martin an abstract (in triplicate) of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 1, 1950.

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CASES SOLICITED FOR REGISTRY OF CARDIOVASCULAR PATHOLOGY

Contribution of cases is being currently solicited for the Registry of Cardiovascular Pathology which has been set up, under the Association's sponsorship, in the American Registry of Pathology at the Armed Forces Institute of Pathology in Washington, D. C. Wallace M. Yater, M.D., is Chairman of the Registry Committee and its other members are Jesse E. Edwards, M.D.; Jane S. Robb, M.D.; Joseph T. Roberts, M.D.; and Helen B. Taussig, M.D. Communications regarding the registry should be addressed to The Director, Armed Forces Institute of Pathology, Washington 25, D. C.

The scope of the Registry is outlined as: a) congenital anomalies of the heart and larger blood vessels; b) subacute bacterial endocarditis; c) the so-called "diseases of the Collagen System" including polyarteritis nodosa, temporal arteritis, disseminated lupus erythematosus, Libman-Sacks endocarditis, scleroderma, and amyloidosis of the heart; d) primary tumors of the heart, pericardium, blood vessels and lymphatics, including rhabdomyomatosis and glycogen-storage disease.

In addition, cases illustrating other diseases of the heart and larger blood vessels, in which consultation is desired or which are of especial interest because of rarity or noteworthy clinico-pathologic correlation will be considered.

1950 RESEARCH GRANTS AND FELLOWSHIPS OF THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for 1950 grants-in-aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$550,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1950-51 will also be received by this Fund up to January 1, 1950. Preference is given to candidates wishing to work in the broad field of cardiovascular function or disease and to candidates wishing to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent, is required. The annual stipend varies, as a rule being between \$3,000 and \$4,000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available.

New grants and fellowships will become available on July 1, 1950.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, N. Y. A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available upon request.

AMERICAN HEART JOURNAL

For the Study of the
CIRCULATION



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PUBLISHED MONTHLY

Under the Editorial Direction of

THE AMERICAN HEART ASSOCIATION

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VOLUME 38

JULY-DECEMBER, 1949

St. Louis

THE C. V. MOSBY COMPANY

1949

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Printed in the
United States of America

Printed at
The C. V. Mosby Company
St. Louis

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